PROTEINS AND NUCLEIC ACIDS ENCODING SAME

RELATED APPLICATIONS

This application claims priority from U.S.S.N. 60/254,329, filed December 8, 2000; U.S.S.N. 60/291,037, filed May 15, 2001; U.S.S.N. 60/255,648, filed December 14, 2000; U.S.S.N. 60/297,173, filed June 8, 2001; U.S.S.N. 60/309,258, filed July 31, 2001; U.S.S.N. 60/326,393, filed October 1, 2001; U.S.S.N. 60/315,639, filed August 29, 2001; each of which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

The invention generally relates to nucleic acids and polypeptides encoded thereby.

BACKGROUND OF THE INVENTION

The invention generally relates to nucleic acids and polypeptides encoded therefrom. More specifically, the invention relates to nucleic acids encoding cytoplasmic, nuclear, membrane bound, and secreted polypeptides, as well as vectors, host cells, antibodies, and recombinant methods for producing these nucleic acids and polypeptides.

SUMMARY OF THE INVENTION

The invention is based in part upon the discovery of nucleic acid sequences encoding novel polypeptides. The novel nucleic acids and polypeptides are referred to herein as NOVX, or NOV1, NOV2, NOV3, NOV4, NOV5, NOV6, NOV7, NOV8, NOV9, NOV10, and NOV11 nucleic acids and polypeptides. These nucleic acids and polypeptides, as well as derivatives, homologs, analogs and fragments thereof, will hereinafter be collectively designated as "NOVX" nucleic acid or polypeptide sequences.

In one aspect, the invention provides an isolated NOVX nucleic acid molecule encoding a NOVX polypeptide that includes a nucleic acid sequence that has identity to the nucleic acids disclosed in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43. In some embodiments, the NOVX nucleic acid molecule will hybridize under stringent conditions to a nucleic acid sequence complementary to a nucleic acid molecule that includes a protein-coding sequence of a NOVX nucleic acid sequence. The

invention also includes an isolated nucleic acid that encodes a NOVX polypeptide, or a fragment, homolog, analog or derivative thereof. For example, the nucleic acid can encode a polypeptide at least 80% identical to a polypeptide comprising the amino acid sequences of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 and 44. The nucleic acid can be, for example, a genomic DNA fragment or a cDNA molecule that includes the nucleic acid sequence of any of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43.

Also included in the invention is an oligonucleotide, *e.g.*, an oligonucleotide which includes at least 6 contiguous nucleotides of a NOVX nucleic acid (*e.g.*, SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43) or a complement of said oligonucleotide.

Also included in the invention are substantially purified NOVX polypeptides (SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 and 44). In certain embodiments, the NOVX polypeptides include an amino acid sequence that is substantially identical to the amino acid sequence of a human NOVX polypeptide.

The invention also features antibodies that immunoselectively bind to NOVX polypeptides, or fragments, homologs, analogs or derivatives thereof.

In another aspect, the invention includes pharmaceutical compositions that include therapeutically- or prophylactically-effective amounts of a therapeutic and a pharmaceutically-acceptable carrier. The therapeutic can be, *e.g.*, a NOVX nucleic acid, a NOVX polypeptide, or an antibody specific for a NOVX polypeptide. In a further aspect, the invention includes, in one or more containers, a therapeutically- or prophylactically-effective amount of this pharmaceutical composition.

In a further aspect, the invention includes a method of producing a polypeptide by culturing a cell that includes a NOVX nucleic acid, under conditions allowing for expression of the NOVX polypeptide encoded by the DNA. If desired, the NOVX polypeptide can then be recovered.

In another aspect, the invention includes a method of detecting the presence of a NOVX polypeptide in a sample. In the method, a sample is contacted with a compound that selectively binds to the polypeptide under conditions allowing for formation of a complex between the polypeptide and the compound. The complex is detected, if present, thereby identifying the NOVX polypeptide within the sample.

The invention also includes methods to identify specific cell or tissue types based on their expression of a NOVX.

Also included in the invention is a method of detecting the presence of a NOVX nucleic acid molecule in a sample by contacting the sample with a NOVX nucleic acid probe or primer, and detecting whether the nucleic acid probe or primer bound to a NOVX nucleic acid molecule in the sample.

In a further aspect, the invention provides a method for modulating the activity of a NOVX polypeptide by contacting a cell sample that includes the NOVX polypeptide with a compound that binds to the NOVX polypeptide in an amount sufficient to modulate the activity of said polypeptide. The compound can be, *e.g.*, a small molecule, such as a nucleic acid, peptide, polypeptide, peptidomimetic, carbohydrate, lipid or other organic (carbon containing) or inorganic molecule, as further described herein.

Also within the scope of the invention is the use of a therapeutic in the manufacture of a medicament for treating or preventing disorders or syndromes including, *e.g.*, Alzheimer's disease, Neurodegenerative disease, Parkinson disease, type 3; Stroke, Parkinson's disease, Huntington's disease, Cerebral palsy, Epilepsy, Ataxia-telangiectasia, Behavioral disorders, Addiction, Anxiety, Pain, Neuroprotection, encephalopathy. pain, psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation, aneurysm, corticoneurogenic disease, gap-junction-related neuropathies and other pathological conditions of the nervous system, where dysfunctions of junctional communication are considered to play a casual role, demyelinating neuropathies (including Charcot-Marie-Tooth disease), Cardiovascular disease, Hemic and Lymphatic Diseases, acute heart failure, hypotension, hypertension, angina pectoris, myocardial infarction, ischemic heart disease, cardiomyopathy, atherosclerosis, congenital heart defects, aortic stenosis , atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus , pulmonary stenosis , subaortic stenosis, ventricular septal defect (VSD), valve diseases, hemophilia, hypercoagulation, idiopathic thrombocytopenic purpura, Erythrokeratodermia variabilis (EKV), atrioventricular (AV) conduction defects such as arrhythmia, and lens cataracts, bone disorders, Muscle Disorders, Alstrom syndrome; Orofacial cleft-2, Preeclampsia; Welander distal myopathy; Von Hippel-Lindau (VHL) syndrome, Tuberous sclerosis, hypercalceimia, Lesch-Nyhan syndrome, Multiple sclerosis, Cell adhesion, shape, interaction communication, cytokinesis disorders; myotonic dystrophy; muscular disorders and diseases; Angelman syndrome, Liddle's syndrome, Prader-Willi syndrome, Kallman syndrome, skin disorders, protease/protease inhibitor deficiency disorders, urinary retention, osteoporosis, Crohn's disease; multiple sclerosis; and Treatment of Albright Hereditary Ostoeodystrophy, ulcers, Dentatorubro-pallidoluysian atrophy(DRPLA) Hypophosphatemic rickets, autosomal

dominant, Peutz-Heghers syndrome, fibromuscular dysplasia, congenital adrenal hyperplasia, endometriosis, cirrhosis, myasthenia gravis, psoriasis, actinic keratosis, excessive hair growth, allopecia, pigmentation disorders, cystitis, incontinence, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, taste and scent detectability disorders, signal transduction pathway disorders, retinal diseases including those involving photoreception, deafness, keratinization disorders, oocyte maturation defects, Myotonia and Cancers including , colon and lung and breast cancer, Leukodystrophies, cancer (especially but not limited to prostate, and skin), Neoplasm; adenocarcinoma; lymphoma, uterus cancer, benign prostatic hypertrophy, enal cancer, multiple endocrine neoplasia type II, familial melanoma, ovarian cancer, adrenoleukodystrophy, Burkitt's lymphoma, Glucosidase I deficiency; severe infantile-onset Wolman disease and milder late onset cholesteryl ester storage disease (CESD), Diabetes, Pancretaitis, Obesity, digetive system disorders, anorexia, bulimia, gastrointestinal polyps, hyperthyroidism, hypothyroidism, endocrine dysfunctions, noninsulin-dependent diabetes mellitus (NIDDM1), immunological disorders and diseases, inflammatory and immune diseases, bacterial, fungal, protozoal and viral infections (particularly infections caused by HIV-1 or HIV-2), asthma, sepsis, graft versus host disease, transplantation, systemic lupus erythematosus, renal tubular acidosis or IgA nephropathy, MHCII and III diseases (immune diseases), hypogonadotropic hypogonadism, reproductive system disorders, infertility, and/or other pathologies and disorders of the like.

The therapeutic can be, *e.g.*, a NOVX nucleic acid, a NOVX polypeptide, or a NOVX-specific antibody, or biologically-active derivatives or fragments thereof.

For example, the compositions of the present invention will have efficacy for treatment of patients suffering from the diseases and disorders disclosed above and/or other pathologies and disorders of the like. The polypeptides can be used as immunogens to produce antibodies specific for the invention, and as vaccines. They can also be used to screen for potential agonist and antagonist compounds. For example, a cDNA encoding NOVX may be useful in gene therapy, and NOVX may be useful when administered to a subject in need thereof. By way of non-limiting example, the compositions of the present invention will have efficacy for treatment of patients suffering from the diseases and disorders disclosed above and/or other pathologies and disorders of the like.

The invention further includes a method for screening for a modulator of disorders or syndromes including, *e.g.*, the diseases and disorders disclosed above and/or other pathologies and disorders of the like. The method includes contacting a test compound with a NOVX polypeptide and determining if the test compound binds to said NOVX polypeptide. Binding

of the test compound to the NOVX polypeptide indicates the test compound is a modulator of activity, or of latency or predisposition to the aforementioned disorders or syndromes.

Also within the scope of the invention is a method for screening for a modulator of activity, or of latency or predisposition to disorders or syndromes including, *e.g.*, the diseases and disorders disclosed above and/or other pathologies and disorders of the like by administering a test compound to a test animal at increased risk for the aforementioned disorders or syndromes. The test animal expresses a recombinant polypeptide encoded by a NOVX nucleic acid. Expression or activity of NOVX polypeptide is then measured in the test animal, as is expression or activity of the protein in a control animal which recombinantly-expresses NOVX polypeptide and is not at increased risk for the disorder or syndrome. Next, the expression of NOVX polypeptide in both the test animal and the control animal is compared. A change in the activity of NOVX polypeptide in the test animal relative to the control animal indicates the test compound is a modulator of latency of the disorder or syndrome.

In yet another aspect, the invention includes a method for determining the presence of or predisposition to a disease associated with altered levels of a NOVX polypeptide, a NOVX nucleic acid, or both, in a subject (*e.g.*, a human subject). The method includes measuring the amount of the NOVX polypeptide in a test sample from the subject and comparing the amount of the polypeptide in the test sample to the amount of the NOVX polypeptide present in a control sample. An alteration in the level of the NOVX polypeptide in the test sample as compared to the control sample indicates the presence of or predisposition to a disease in the subject. Preferably, the predisposition includes, *e.g.*, the diseases and disorders disclosed above and/or other pathologies and disorders of the like. Also, the expression levels of the new polypeptides of the invention can be used in a method to screen for various cancers as well as to determine the stage of cancers.

In a further aspect, the invention includes a method of treating or preventing a pathological condition associated with a disorder in a mammal by administering to the subject a NOVX polypeptide, a NOVX nucleic acid, or a NOVX-specific antibody to a subject (*e.g.*, a human subject), in an amount sufficient to alleviate or prevent the pathological condition. In preferred embodiments, the disorder, includes, *e.g.*, the diseases and disorders disclosed above and/or other pathologies and disorders of the like.

In yet another aspect, the invention can be used in a method to identity the cellular receptors and downstream effectors of the invention by any one of a number of techniques

commonly employed in the art. These include but are not limited to the two-hybrid system, affinity purification, co-precipitation with antibodies or other specific-interacting molecules.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel nucleotides and polypeptides encoded thereby. Included in the invention are the novel nucleic acid sequences and their encoded polypeptides. The sequences are collectively referred to herein as "NOVX nucleic acids" or "NOVX polynucleotides" and the corresponding encoded polypeptides are referred to as "NOVX polypeptides" or "NOVX proteins." Unless indicated otherwise, "NOVX" is meant to refer to any of the novel sequences disclosed herein. Table A provides a summary of the NOVX nucleic acids and their encoded polypeptides.

TABLE A. Sequences and Corresponding SEQ ID Numbers

NOVX Assignment	Internal Identification	SEQ ID NO (nucleic acid)	SEQ ID NO (polypeptide)	Homology
1a	146642892/CG50377-01	1	2	Cub and Sushi Domain-Containing Protein
1b	CG50377-02	3	4	Cub and Sushi Domain-Containing Protein
2	cg-118733234	5	6	Myelin-like protein
3	cg-122561227	7	8	von Willebrand Factor and Kielin-like protein
4a	SC70504370_A/CG59253-01	9	10	Semaphorin-like protein
4b	CG59253-02	11	12	Semaphorin 6A1 (KIAA1479)-like protein
4c	CG59253-05	13	14	Semaphorin-like protein
4d	CG59253-06	15	16	Semaphorin-like protein
4e	CG59253-07	17	18	Semaphorin-like protein

4f	CG59253-08	19	20	Semaphorin-like protein
5a	CG50211-01	21	22	serine/threonine protein kinase-like protein
5b	CG50211-02	23	24	serine/threonine protein kinase-like protein
6a	CG50215-01	25	26	TGF-beta binding protein
6b	CG50215-03	27	28	TGF-beta binding protein
6c	CG50215-04	29	30	TGF-beta binding protein
6d	CG50215-05	31	32	TGF-beta binding protein
7	GMAP000808_A_da1	33	34	MAS PROTO-ONCOGENE-like protein
8	AL163195_da2	35	36	RIBONUCLEASE PANCREATIC PRECURSOR-like protein
9	SC87421058_A	37	38	AMINOTRANSFERASE-like protein
10a	CG50235-01	39	40	Tolloid-Like 2-like protein
10b	CG50235-03	41	42	Tolloid-Like 2-like protein
11	SC135004534_A	43	44	CYSTEINE SULFINIC ACID DECARBOXYLASE -like protein

NOVX nucleic acids and their encoded polypeptides are useful in a variety of applications and contexts. The various NOVX nucleic acids and polypeptides according to the invention are useful as novel members of the protein families according to the presence of domains and sequence relatedness to previously described proteins. Additionally, NOVX nucleic acids and polypeptides can also be used to identify proteins that are members of the family to which the NOVX polypeptides belong.

NOV1 is homologous to a Cub and Sushi Domain-containing-like family of proteins. Thus, the NOV1 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example; cancer, obesity, inflammation, hypertension, neurological diseases, neuropsychiatric diseases, small stature, obesity, diabetes, hyperlipidemia and other diseases, disorders and conditions of the like.

NOV2 is homologous to the myelin-like family of proteins. Thus NOV2 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example; cancer, inflammation, neurological disorders, neuropsychiatric disorders, obesity, diabetes and other diseases, disorders and conditions of the like.

NOV3 is homologous to a family of von Willebrand Factor-like and Kielin-like proteins. Thus, the NOV3 nucleic acids and polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: cancer, inflammation, neurological disorders, neuropsychiatric disorders, obesity, diabetes, bleeding disorders and other diseases, disorders and conditions of the like.

NOV4 is homologous to the semaphorin-like family of proteins. Thus, NOV4 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: Parkinson's disease , psychotic and neurological disorders, Alzheimers disease, Lung and other cancers and other diseases, disorders and conditions of the like.

NOV5 is homologous to the serine/threonine kinase-like family of proteins. Thus NOV5 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in systemic lupus erythematosus, autoimmune disease, asthma, emphysema, scleroderma, ARDS, fertility, endometriosis, hemophilia, hypercoagulation, idiopathic thrombocytopenic purpura, allergies, immunodeficiencies, transplantation, graft versus host disease (GVHD), lymphaedema, muscular dystrophy, Lesch-Nyhan syndrome, myasthenia gravis, psoriasis, actinic keratosis, tuberous sclerosis, acne, hair growth/loss, allopecia, pigmentation disorders, endocrine disorders, Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, hypercalceimia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neuroprotection, tonsilitis and other diseases, disorders and conditions of the like.

NOV6 is homologous to the TGF-beta-like family of proteins. Thus NOV6 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: atherosclerosis and fibrotic disease of the kidney, liver, and lung, cancer (*e.g.* epithelial, endothelial, and hematopoietic), hereditary hemorrhagic telangiectasia. and other diseases, disorders and conditions of the like.

NOV7 is homologous to members of the MAS proto-oncogene-like family of proteins. Thus, the NOV7 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example; Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, tuberous sclerosis, hypercalceimia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neuroprotection, neurological disorders and diseases involving developmental and other diseases, disorders and conditions of the like.

NOV8 is homologous to the ribonuclease pancreatic precursor-like family of proteins. Thus, NOV8 nucleic acids and polypeptides, antibodies and related compounds according to

the invention will be useful in therapeutic and diagnostic applications implicated in, for example; anti-cancer and anti-tumor therapy, diabetes,Von Hippel-Lindau (VHL) syndrome, pancreatitis, obesity, hyperthyroidism and hypothyroidism and hancers including, but no limited to thyroid and pancreas, and other diseases, disorders and conditions of the like.

NOV9 is homologous to the aminotransferase-like family of proteins. Thus, NOV9 nucleic acids and polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example; liver toxicity and damage such as in cancer, cirrhosis, or troglitazone treatment for diabetes; brain and CNS disorders including cancer, Parkinson's, Alzheimer's, epilepsy, schizophrenia and other diseases, disorders and conditions of the like.

NOV10 is homologous to the tolloid-like-2-like family of proteins. Thus, NOV10 nucleic acids and polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example; fibrosis, scarring, keloids, surgical adhesion, wound and fracture healing, and other diseases, disorders and conditions of the like.

NOV11 is homologous to the cysteine sulfinic acid decarboxylase-like family of proteins. Thus, NOV11 nucleic acids and polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example; acute or chronic hyperosmotic plasma, Adrenoleukodystrophy , Congenital Adrenal Hyperplasia, Diabetes,Von Hippel-Lindau (VHL) syndrome , Pancreatitis, Obesity, Hyperparathyroidism, Hypoparathyroidism, Fertility, cancers such as those occurring in pancreas, bone, colon, brain, lung, breast, or prostate. Endometriosis, Xerostomia Scleroderma Hypercalceimia, Ulcers Von Hippel-Lindau (VHL) syndrome, Cirrhosis,Transplantation, Inflammatory bowel disease, Diverticular disease, Hirschsprung's disease , Crohn's Disease, Appendicitis Osteoporosis, Hypercalceimia, Arthritis, Ankylosing spondylitis, Scoliosis Arthritis, Tendinitis on Hippel-Lindau (VHL) syndrome , Alzheimer's disease, Stroke, Tuberous sclerosis, hypercalceimia, Parkinson's disease, Huntington's disease, Cerebral palsy, Epilepsy, Lesch-Nyhan syndrome, Multiple sclerosis,Ataxia-telangiectasia, Leukodystrophies, Behavioral disorders, Addiction, Anxiety, Pain, Endocrine dysfunctions, Diabetes, obesity, Growth and reproductive disorders Multiple sclerosis, Leukodystrophies, Pain, Myasthenia gravis, Pain, Systemic lupus erythematosus , Autoimmune disease, Asthma, Emphysema, Scleroderma, allergy, ARDS, Psoriasis, Actinic keratosis ,Tuberous sclerosis, Acne, Hair growth, allopecia, pigmentation disorders, Renal artery stenosis, Interstitial nephritis, Glomerulonephritis, Polycystic kidney disease, Systemic

lupus erythematosus, Renal tubular acidosis, IgA nephropathy, Hypercalceimia, Lesch-Nyhan syndrome and other diseases, disorders and conditions of the like.

The NOVX nucleic acids and polypeptides can also be used to screen for molecules, which inhibit or enhance NOVX activity or function. Specifically, the nucleic acids and polypeptides according to the invention may be used as targets for the identification of small molecules that modulate or inhibit, *e.g.*, neurogenesis, cell differentiation, cell proliferation, hematopoiesis, wound healing and angiogenesis.

Additional utilities for the NOVX nucleic acids and polypeptides according to the invention are disclosed herein.

NOV1

NOV1 includes two cub and sushi domain containing protein-like proteins disclosed below. The disclosed sequences have been named NOV1a and NOV1b.

NOV1a

A disclosed NOV1a nucleic acid of 10,136 nucleotides (also referred to as 146642892/CG50377-01) encoding a novel Cub and Sushi Domain-Containing Protein-like protein is shown in Table 1A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 1-3 and ending with a TGA codon at nucleotides 9313-9315. A putative untranslated region upstream from the initiation codon and downstream from the termination codon is underlined in Table 1A. The start and stop codons are in bold letters.

Table 1A. NOV1a nucleotide sequence (SEQ ID NO:1).

ATGGCGGGCGCCCCTCCCCCCGCCTTGCTGCTGCCTTGCAGTTTGATCTCAGACTGCTGTGCTAGCAATC
AGCGACACTCCGTGGGCGTAGGACCCTCCGAGCTAGTCAAGAAGCAAATTGAGTTGAAGTCTCGAGGTGT
GAAGCTGATGCCCAGCAAAGACAACAGCCAGAAGACGTCTGTGTTAACTCAGGTTGGTGTGTCCCAAGGA
CATAATATGTGTCCAGACCCTGGCATACCCGAAAGGGGCAAAAGACTAGGCTCGGATTTCAGGTTAGGAT
CCAGCGTCCAGTTCACCTGCAACGAGGGCTATGACCTGCAAGGGTCCAAGCGGATCACCTGTATGAAAGT
GAGCGACATGTTTGCGGCCTGGAGCGACCACAGGCCAGTCTGCCGAGCCCGCATGTGTGATGCCCACCTT
CGAGGCCCCTCGGGCATCATCACCTCCCCCAATTTCCCCATTCAGTATGACAACAATGCACACTGTGTGT
GGATCATCACAGCACTCAACCCCTCCAAGGTGATCAAGCTCGCCTTTGAGGAGTTTGATTTGGAGAGGGG
CTATGACACCCTGACGGTCGGTGATGGTGGTCAGGATGGGGACCAGAAGACAGTTCTCTACATGTCTCAA
AATGCCTGCAGTGACAGCCCTCACACCCCAGGCTCTCGCATCCCAGAGAGCATGTCTGGGGACATCTGGA
GGCAGAAATGGACTGTACTTGAGATCTGTCGTGACATTAGCAGTTCAGATGCAAGGTCAGGTTCAGTGAG
GAAGTCTCCAAAGACTTCTAATGCTGTGGAACTTGTTGCTCCTGGGACAGAGATCGAGCAGGGCAGTTGC
GGTGACCCTGGCATACCTGCATATGGCCGGAGGGAAGGCTCCCGGTTTCACCACGGTGACACACTCAAGT
TTGAGTGCCAGCCCGCCTTTGAGCTGGTGGGACAGAAGGCAATCACATGCCAAAAGAATAACCAATGGTC
GGCTAAGAAGCCAGGCTGCGTGTTCTCCTGCTTCTTCAACTTCACCAGCCCGTCTGGGGTTGTCCTGTCT
CCCAACTACCCAGAGGACTATGGCAACCACCTCCACTGTGTCTGGCTCATCCTGGCCAGGCCTGAGAGCC
GCATCCACCTGGCCTTCAACGACATTGACGTGGAGCCTCAGTTTGATTTCCTGGTCATCAAGGATGGGGC
CACCGCCGAGGCGCCCGTCCTGGGCACCTTCTCAGGAAACCAGCTTCCCTCCTCCATCACAAGCAGTGGC
CACGTGGCCCGTCTCGAGTTCCAGACTGACCACTCCACAGGGAAGAGGGGCTTCAACATCACTTTTACCA
CCTTCCGACACAACGAGTGCCCGGATCCTGGCGTTCCAGTAAATGGCAAACGGTTTGGGGACAGCCTCCA
GCTGGGCAGCTCCATCTCCTTCCTCTGTGATGAAGGCTTCCTTGGGACTCAGGGCTCAGAGACCATCACC
TGCGTCCTGAAGGAGGGCAGCGTGGTCTGGAACAGCGCTGTGCTGCGGTGTGAAGCTCCCTGTGGTGGTC
ACCTGACTTCGCCCAGCGGCACCATCCTCTCTCCGGGCTGGCCTGGCTTCTACAAGGATGCCTTGAGCTG
TGCCTGGGTGATTGAGGCCCAGCCAGGCTACCCCATCAAAATCACCTTCGACAGATTCAAAACCGAGGTC

AACTATGACACCCTGGAAGTACGCGATGGGCGGACTTACTCAGCGCCCTTGATCGGGGTTTACCACGGGA
CCCAGGTTCCCCAGTTCCTCATCAGCACCAGCAACTACCTCTACCTCCTCTTCTCTACCGACAAGAGTCA
CTCGGACATCGGCTTCCAGCTCCGCTATGAGACTATAACACTGCAGTCAGACCACTGTCTGGATCCAGGA
ATCCCAGTAAATGGACAGCGTCATGGGAATGACTTCTACGTGGGCGCGCTGGTGACCTTCAGCTGTGACT
CGGGCTACACATTAAGTGACGGGGAGCCTCTGGAGTGTGAGCCCAACTTCCAGTGGAGCCGGGCCCTGCC
CAGTTGTGAAGCTCTCTGTGGTGGCTTCATTCAAGGCTCCAGTGGGACCATCTTGTCGCCAGGGTTCCCT
GACTTCTACCCCAACAACTTGAACTGCACCTGGATTATCGAAACATCTCATGGCAAGGGTGTGTTCTTCA
CTTTCCACACCTTCCACCTGGAAAGTGGCCATGACTACCTCCTCATCACTGAGAACGGCAGCTTCACCCA
GCCCCTGAGGCAGCTAACTGGATCTCGGCTGCCAGCTCCCATCAGCGCTGGGCTCTATGGCAACTTCACT
GCCCAGGTCCGCTTCATCTCTGATTTCTCCATGTCATATGAAGGATTCAACATCACCTTCTCAGAGTACG
ACTTGGAGCCCTGTGAGGAGCCCGAGGTCCCAGCCTACAGCATCCGGAAGGGCTTGCAGTTTGGCGTGGG
CGACACCTTGACCTTCTCCTGCTTCCCCGGGTACCGTCTGGAGGGCACCGCCCGCATCACGTGCCTGGGG
GGCAGACGGCGCCTGTGGAGCTCGCCTCTGCCAAGGTGTGTTGCTGAGTGTGGGAATTCAGTCACAGGCA
CTCAGGGTACTTTGCTGTCCCCCAACTTTCCTGTGAACTACAATAACAATCATGAATGCATCTACTCCAT
CCAGACCCAGCCAGGGAAGGGAATTCAGCTGAAAGCCAGGGCATTCGAACTCTCCGAAGGAGATGTCCTC
AAGGTTTATGATGGCAACAACAACTCCGCCCGTTTGCTGGGAGTTTTTAGCCATTCTGAGATGATGGGGG
TGACTTTGAACAGCACATCCAGCAGTCTGTGGCTTGATTTCATCACTGATGCTGAAAACACCAGCAAGGG
CTTTGAACTGCACTTTTCCAGCTTTGAACTCATCAAATGTGAGGACCCAGGAACCCCCAAGTTTGGCTAC
AAGGTTCATGATGAAGGTCATTTTGCAGGGAGCTCCGTGTCCTTCAGCTGTGACCCTGGATACAGCCTGC
GGGGTAGTGAGGAGCTGCTGTGTCTGAGTGGAGAGCGCCGGACCTGGGACCGGCCTCTGCCCACCTGTGT
CGCCGAGTGTGGAGGGACAGTGAGAGGAGAGGTGTCGGGGCAGGTGCTGTCACCCGGGTATCCAGCTCCC
TATGAACACAATCTCAACTGCATCTGGACCATCGAAGCAGAGGCCGGCTGCACCATTGGGCTACACTTCC
TGGTGTTTGACACAGAGGAGGTTCACGACGTGCTGCGCATCTGGGATGGGCCTGTGGAGAGCGGGGTTCT
GCTGAAGGAGCTGAGTGGCCCGGCCCTGCCCAAGGACCTGCATAGCACCTTCAACTCGGTCGTCCTGCAG
TTCAGCACTGACTTCTTCACCAGCAAGCAGGGCTTTGCCATTCAATTTTCAGTGTCCACAGCAACGTCCT
GCAATGACCCTGGGATCCCGCAGAATGGGAGTCGGAGTGGTGACAGTTGGGAAGCCGGCGACTCCACAGT
GTTCCAGTGTGACCCTGGCTACGCGCTGCAGGGAAGTGCAGAGATCAGCTGTGTGAAGATCGAGAACAGG
TTCTTCTGGCAGCCCAGCCCGCCAACATGCATCGCTCCCTGCGGGGGAGACCTGACAGGACCATCTGGAG
TCATCCTCTCACCAAATTACCCAGAACCCTACCCGCCAGGCAAGGAGTGTGACTGGAAAGTGACCGTCTC
ACCAGACTACGTCATCGCCCTGGTATTTAACATCTTTAACCTGGAGCCTGGCTATGACTTCCTCCATATC
TACGACGGACGGGACTCTCTCAGCCCTCTCATAGGAAGCTTCTATGGCTCCCAGCTCCCAGGCCGCATTG
AAAGCAGCAGCAACAGCCTCTTCCTCGCCTTCCGCAGCGATGCATCTGTGAGCAATGCTGGCTTCGTCAT
TGACTATACAGAAAACCCGCGGGAGTCATGTTTTGATCCTGGTTCCATCAAGAACGGCACACGGGTGGGG
TCCGACCTGAAGCTGGGCTCCTCCGTCACCTACTACTGCCACGGGGGCTACGAAGTTGAGGGCACCTCGA
CCCTGAGCTGCATCCTGGGGCCTGATGGGAAGCCCGTGTGGAACAATCCCCGGCCAGTCTGCACAGCCCC
CTGTGGGGGACAGTATGTGGGTTCGGACGGAGTGGTCTTGTCCCCCAACTACCCCCAGAACTACACCAGT
GGACAGATCTGCTTGTATTTTGTTACTGTGCCCAAGGACTATGTGGTGTTTGGCCAGTTCGCCTTCTTTC
ACACGGCCCTCAACGACGTGGTGGAGGTTCACGACGGCCACAGCCAGCACTCGCGGCTCCTCAGCTCCCT
CTCGGGCTCCCATACAGGAGAATCACTGCCCTTGGCCACCTCCAATCAAGTTCTCATTAAGTTCAGCGCC
AAAGGCCTCGCACCAGCCAGAGGCTTCCACTTTGTCTACCAAGCGGTTCCTCGAACCAGCGCCACGCAGT
GCAGCTCTGTGCCGGAACCCCGCTATGGCAAGAGGCTGGGCAGTGACTTCTCGGTGGGGGCCATCGTCCG
CTTCGAATGCAACTCCGGCTATGCCCTGCAGGGGTCGCCAGAGATCGAGTGCCTCCCTGTGCCTGGGGCC
TTGGCCCAATGGAATGTCTCAGCGCCCACGTGTGTGGTGCCGTGTGGAGGCAACCTCACAGAGCGCAGGG
GCACCATCCTGTCCCCTGGCTTCCCAGAGCCGTACCTCAACAGCCTCAACTGTGTGTGGAAGATCGTGGT
CCCCGAAGGCGCTGGCATCCAGATCCAAGTTGTCAGTTTTGTGACAGAGCAGAACTGGGACTCGCTGGAA
GTATTTGATGGTGCAGATAACACTGTAACCATGCTGGGGAGTTTCTCAGGAACAACCGTGCCTGCCCTTC
TGAACAGCACCTCCAACCAGCTCTACCTTCATTTCTACTCAGATATCAGCGTATCTGCAGCTGGCTTCCA
CTTGGAGTACAAAACGGTGGGCCTGAGCAGTTGTCCGGAACCTGCTGTGCCCAGTAACGGGGTGAAGACT
GGCGAGCGCTACTTGGTGAATGATGTGGTGTCTTTCCAGTGTGAGCCGGGATATGCCCTCCAGGGCCACG
CCCACATCTCCTGCATGCCCGGAACAGTGCGGCGATGGAACTACCCTCCTCCACTCTGTATTGCACAGTG
TGGGGGAACAGTGGAGGAGATGGAGGGGGTGATCCTGAGCCCCGGCTTCCCAGGCAACTACCCCAGTAAC
ATGGACTGCTCCTGGAAAATAGCACTGCCCGTGGGCTTTGGAGCTCACATCCAGTTCCTGAACTTCTCCA
CCGAGCCCAACCACGACTACATAGAAATCCGGAATGGCCCCTATGAGACCAGCCGCATGATGGGAAGATT
CAGTGGAAGCGAGCTTCCAAGCTCCCTCCTCTCCACGTCCCACGAGACCACCGTGTATTTCCACAGCGAC
CACTCCCAGAATCGGCCAGGATTCAAGCTGGAGTATCAGGCCTATGAACTTCAAGAGTGCCCAGACCCAG
AGCCCTTTGCCAATGGCATTGTGAGGGGAGCTGGCTACAACGTGGGACAATCAGTGACCTTCGAGTGCCT
CCCGGGGTATCAATTGACTGGCCACCCTGTCCTCACGTGTCAACATGGCACCAACCGGAACTGGGACCAC
CCCCTGCCCAAGTGTGAAGTCCCTTGTGGCGGGAACATCACTTCTTCCAACGGCACTGTGTACTCCCCGG
GGTTCCCTAGCCCGTACTCCAGCTCCCAGGACTGTGTCTGGCTGATCACCGTGCCCATTGGCCATGGCGT
CCGCCTCAACCTCAGCCTGCTGCAGACAGAGCCCTCTGGAGATTTCATCACCATCTGGGATGGGCCACAG
CAAACAGCACCACGGCTCGGCGTCTTCACCCGGAGCATGGCCAAGAAAACAGTGCAGAGTTCATCCAACC
AGGTCCTGCTCAAGTTCCACCGTGATGCAGCCACAGGGGGATCTTCGCCATAGCTTTCTCCGCTTATCC
ACTCACCAAATGCCCTCCTCCCACCATCCTCCCCAACGCCGAAGTCGTCACAGAGAATGAAGAATTCAAT
ATAGGTGACATCGTACGCTACAGATGCCTCCCTGGCTTTACCTTAGTGGGGAATGAAATTCTGACCTGCA
AACTTGGAACCTACCTGCAGTTTGAAGGACCACCCCCGATATGTGAAGTGCACTGTCCAACAAATGAGCT
TCTGACAGACTCCACAGGCGTGATCCTGAGCCAGAGCTACCCTGGAAGCTATCCCCAGTTCCAGACCTGC
TCTTGGCTGGTGAGAGTGGAGCCCGACTATAACATCTCCCTCACAGTGGAGTACTTCCTCAGCGAGAAGC
AATATGATGAGTTTGAGATTTTTGATGGTCCATCAGGACAGAGTCCTCTGCTGAAAGCCCTCAGTGGGAA
TTACTCAGCTCCCCTGATTGTCACCAGCTCAAGCAACTCTGTGTACCTGCGTTGGTCATCTGATCACGCC

TACAATCGGAAGGGCTTCAAGATCCGCTATTCAGCCCCTTACTGCAGCCTGCCCAGGGCTCCACTCCATG
GCTTCATCCTAGGCCAGACCAGCACCCAGCCCGGGGGCTCCATCCACTTTGGCTGCAACGCCGGCTACCG
CCTGGTGGGACACAGCATGGCCATCTGTACCCGGCACCCCCAGGGCTACCACCTGTGGAGCGAAGCCATC
CCTCTCTGTCAAGCTCTTTCCTGTGGGCTTCCTGAGGCCCCCAAGAATGGAATGGTGTTTGGCAAGGAGT
ACACAGTGGGAACCAAGGCCGTGTACAGCTGCAGTGAAGGCTACCACCTCCAGGCAGGCGCTGAGGCCAC
TGCAGAGTGTCTGGACACAGGCCTATGGAGCAACCGCAATGTCCCACCACAGTGTGTCCCTGTGACTTGT
CCTGATGTCAGTAGCATCAGCGTGGAGCATGGCCGATGGAGGCTTATCTTTGAGACACAGTATCAGTTCC
AGGCCCAGCTGATGCTCATCTGTGACCCTGGCTACTACTATACTGGCCAAAGGGTCATCCGCTGTCAGGC
CAATGGCAAATGGAGCCTCGGGGACTCTACGCCCACCTGCCGAATCATCTCCTGTGGAGAGCTCCCGATT
CCCCCCAATGGCCACCGCATCGGAACACTGTCTGTCTACGGGGCAACAGCCATCTTCTCCTGCAATTCCG
GATACACACTGGTGGGCTCCAGGGTGCGTGAGTGCATGGCCAATGGGCTCTGGAGTGGCTCTGAAGTCCG
CTGCCTTGCTGGACACTGTGGGACTCCTGAGCCCATTGTCAACGGACACATCAATGGGGAGAACTACAGC
TACCGGGGCAGTGTGGTGTACCAATGCAATGCTGGCTTCCGCCTGATCGGCATGTCTGTGCGCATCTGCC
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TGTCAACGGCCTCACTCAGGGTAACCAGTTTAACCTCAACGATGTGGTCAAGTTTGTTTGCAACCCTGGG
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GCAGAATCATCAACTGTACAGATCCTGGACACCAAGAAAATAGTGTTCGTCAGGTCCACGCCAGCGGCCC
GCACAGGTTCAGCTTCGGCACCACTGTGTCTTACCGGTGCAACCACGGCTTCTACCTCCTGGGCACCCCA
GTGCTCAGCTGCCAGGGAGATGGCACATGGGACCGTCCCCGCCCCCAGTGTCTCTTGGTGTCCTGTGGCC
ATCCGGGCTCCCCGCCTCACTCCCAGATGTCTGGAGACAGTTATACTGTGGGAGCAGTGGTGCGGTACAG
CTGCATCGGCAAGCGTACTCTGGTGGGAAACAGCACCCGCATGTGTGGGCTGGATGGACACTGGACTGGC
TCCCTCCCTCACTGCTCAGGAACCAGCGTGGGAGTTTGCGGTGACCCTGGGATCCCGGCTCATGGCATCC
GTTTGGGGGACAGCTTTGATCCAGGCACTGTGATGCGCTTCAGCTGTGAAGCTGGCCACGTGCTCCGGGG
ATCGTCAGAGCGCACCTGTCAAGCCAATGGCTCGTGGAGCGGCTCGCAGCCTGAGTGTGGAGTGATCTCT
TGTGGGAACCCTGGGACTCCAAGTAATGCCCGAGTTGTGTTCAGTGATGGCCTGGTTTTCTCCAGCTCTA
TCGTCTATGAGTGCCGGGAAGGATACTACGCCACAGGCCTGCTCAGCCGTCACTGCTCGGTCAATGGTAC
CTGGACAGGCAGTGACCCTGAGTGCCTCGTCATAAACTGTGGTGACCCTGGGATTCCAGCCAATGGCCTT
CGGCTGGGCAATGACTTCAGGTACAACAAAACTGTGACATATCAGTGTGTCCCTGGCTATATGATGGAGT
CACATAGAGTATCTGTGCTGAGCTGCACCAAGGACCGGACATGGAATGGAACCAAGCCCGTCTGCAAAGC
TCTCATGTGCAAGCCACCTCCGCTCATCCCCAATGGGAAGGTGGTGGGGTCTGACTTCATGTGGGGCTCA
AGTGTGACTTATGCCTGCCTGGAGGGGTACCAGCTCTCCCTGCCCGCGGTGTTCACCTGTGAGGGAAATG
GGTCCTGGACCGGAGAGCTGCCTCAGTGTTTCCCTGTGTTCTGCGGGGATCCTGGTGTCCCGTCCCGTGG
GAGGAGAGGACCGAGGCTTCTCCTACAGGTCATCTGTCTCCTTCTCCTGCCATCCCCCTCTGGTGCTG
GTGGGCTCTCCACGCAGGTTTTGCCAGTCAGATGGGACATGGAGTGGCACCCAGCCCAGCTGCATAGATC
CGACCCTGACCACGTGTGCGGACCCTGGTGTGCCACAGTTTGGGATACAGAACAATTCTCAGGGCTACCA
GGTTGGAAGCACAGTCCTCTTCCGTTGTCAAAAAGGCTACCTGCTTCAGGGCTCCACCACCAGGACCTGC
CTCCCAAACCTGACCTGGAGTGGAACCCCACCTGACTGTGTCCCCCACCACTGCAGGCAGCCAGAGACGC
CAACGCATGCCAACGTCGGGGCCCTGGATTTGCCCTCCATGGGCTACACGCTCATTACTCCTGCCAGGAG
GGCTTCTCCCTCAAGGGTGGCTCCGAGCACCGCACCTGCAAGGCGGATGGCAGCTGGACAGGCAAGCCGC
CCATCTGCCTGGAGGTCCGGCCCAGTGGGAGACCCATCAACACTGCCCGGGAGCCACCGCTCACCCAAGC
CT**TGA**TTCCTGGGGATGTTTTTGCCAAGAATTCCCTGTGGAAAGGGGCCTATGAATACCAGGGGAAGAAG
CAGCCAGCCATGCTCAGAGTGACTGGCTTCCAAGTTGCCAACAGCAAGGTCAATGCCACCATGATCGACC
ACAGTGGCGTGGAGCTGCACTTGGCTGGAACTTACAAGAAAGAAGATTTTCATCTCCTACTCCAGGTGTA
CCAGATTACAGGGCCTGTGGAGATCTTTATGAATAAGTTCAAAGATGATCACTGGGCTTTAGATGGCCAT
GTCTCGTCAGAGTCCTCCGGAGCCACCTTCATCTACCAAGGCTCTGTCAAGGGCCAAGGCTTTGGGCAGT
TCGGCTTTCAAAGACTGGACCTCAGGCTGCTGGAGTCAGACCCCGAGTCCATTGGCCGCCACTTTGCTTC
CAACAGCAGCTCAGTGGCAGCCGCGATCCTGGTGCCTTTCATCGCCCTCATTATTGCGGGCTTCGTGCTC
TATCTCTACAAGCACAGGAGAAGACCCAAAGTTCCTTTCAATGGCTATGCTGGCCACGAGAACACCAATG
TTCGGGCCACATTTGAGAACCCAATGTACGACCGCAACATCCAGCCCACAGACATCATGGCCAGCGAGGC
GGAGTTCACAGTCAGCACAGTGTGCACAGCAGTATAGCCACCCGGCCTGGCCGCTTTTTTTGCTAGGTTG
AACTGGTACTCCAGCAGCCGCCGAAGCTGGACTGTACTGCTGCCATCTCAGCTCACTGCAACCTCCCTGC
CTGATTCCCCTGCCTCAGCCTGCCGAGTGCCTGCGATTGCAGGCGCGCACCGCCAC

In a search of public sequence databases, the NOV1a nucleic acid sequence, located on chromsome 1 257 of 259 bases (99%) identical to a gb:GENBANK-ID: AK022620|acc: AK022620.1 mRNA from Homo sapiens (Homo sapiens cDNA FLJ12558 fis, clone NT2RM4000787). Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

In all BLAST alignments herein, the "E-value" or "Expect" value is a numeric indication of the probability that the aligned sequences could have achieved their similarity to the BLAST query sequence by chance alone, within the database that was searched. For

example, the probability that the subject ("Sbjct") retrieved from the NOV1 BLAST analysis, *e.g.*, *Homo sapiens* cDNA FLJ12558 fis, matched the Query NOV1 sequence purely by chance is 1.1e -47. The Expect value (E) is a parameter that describes the number of hits one can "expect" to see just by chance when searching a database of a particular size. It decreases exponentially with the Score (S) that is assigned to a match between two sequences. Essentially, the E value describes the random background noise that exists for matches between sequences.

The Expect value is used as a convenient way to create a significance threshold for reporting results. The default value used for blasting is typically set to 0.0001. In BLAST 2.0, the Expect value is also used instead of the P value (probability) to report the significance of matches. For example, an E value of one assigned to a hit can be interpreted as meaning that in a database of the current size one might expect to see one match with a similar score simply by chance. An E value of zero means that one would not expect to see any matches with a similar score simply by chance. See, e.g., http://www.ncbi.nlm.nih.gov/Education/BLASTinfo/. Occasionally, a string of X's or N's will result from a BLAST search. This is a result of automatic filtering of the query for low-complexity sequence that is performed to prevent artifactual hits. The filter substitutes any low-complexity sequence that it finds with the letter "N" in nucleotide sequence (e.g., "NNNNNNNNNNNN") or the letter "X" in protein sequences (e.g., "XXXXXXXXX"). Low-complexity regions can result in high scores that reflect compositional bias rather than significant position-by-position alignment. (Wootton and Federhen, Methods Enzymol 266:554-571, 1996).

The disclosed NOV1a polypeptide (SEQ ID NO:2) encoded by SEQ ID NO:1 has 3104 amino acid residues and is presented in Table 1B using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV1a has a signal peptide and is likely to be localized outside the cell with a certainty of 0.3700. In other embodiments, NOV1a may also be localized to the lysome (lumen) with a certainty of 0.1900, the microbody with a certainty or 0.1764, or in the endoplasmic reticulum (membrane) with a certainty of 0.1000. The most likely cleavage site for a NOV1a peptide is between amino acids 21 and 22, at: CCA-SN.

Table 1B. Encoded NOV1a protein sequence (SEQ ID NO:2).

```
MAGAPPPALLLPCSLISDCCASNQRHSVGVGPSELVKKQIELKSRGVKLMPSKDNSQKTSVLTQVGVSQG
HNMCPDPGIPERGKRLGSDFRLGSSVQFTCNEGYDLQGSKRITCMKVSDMFAAWSDHRPVCRARMCDAHL
RGPSGIITSPNFPIQYDNNAHCVWIITALNPSKVIKLAFEEFDLERGYDTLTVGDGGQDGDQKTVLYMSQ
NACSDSPHTPGSRIPESMSGDIWRQKWTVLEICRDISSSDARSGSVRKSPKTSNAVELVAPGTEIEQGSC
GDPGIPAYGRREGSRFHHGDTLKFECQPAFELVGQKAITCQKNNQWSAKKPGCVFSCFFNFTSPSGVVLS
PNYPEDYGNHLHCVWLILARPESRIHLAFNDIDVEPQFDFLVIKDGATAEAPVLGTFSGNQLPSSITSSG
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HVARLEFQTDHSTGKRGFNITFTTFRHNECPDPGVPVNGKRFGDSLQLGSSISFLCDEGFLGTQGSETIT
CVLKEGSVVWNSAVLRCEAPCGGHLTSPSGTILSPGWPGFYKDALSCAWVIEAQPGYPIKITFDRFKTEV
NYDTLEVRDGRTYSAPLIGVYHGTQVPQFLISTSNYLYLLFSTDKSHSDIGFQLRYETITLQSDHCLDPG
IPVNGQRHGNDFYVGALVTFSCDSGYTLSDGEPLECEPNFQWSRALPSCEALCGGFIQGSSGTILSPGFP
DFYPNNLNCTWIIETSHGKGVFFTFHTFHLESGHDYLLITENGSFTQPLRQLTGSRLPAPISAGLYGNFT
AQVRFISDFSMSYEGFNITFSEYDLEPCEEPEVPAYSIRKGLQFGVGDTLTFSCFPGYRLEGTARITCLG
GRRRLWSSPLPRCVAECGNSVTGTQGTLLSPNFPVNYNNNHECIYSIQTQPGKGIQLKARAFELSEGDVL
KVYDGNNNSARLLGVFSHSEMMGVTLNSTSSSLWLDFITDAENTSKGFELHFSSFELIKCEDPGTPKFGY
KVHDEGHFAGSSVSFSCDPGYSLRGSEELLCLSGERRTWDRPLPTCVAECGGTVRGEVSGQVLSPGYPAP
YEHNLNCIWTIEAEAGCTIGLHFLVFDTEEVHDVLRIWDGPVESGVLLKELSGPALPKDLHSTFNSVVLQ
FSTDFFTSKQGFAIQFSVSTATSCNDPGIPQNGSRSGDSWEAGDSTVFQCDPGYALQGSAEISCVKIENR
FFWQPSPPTCIAPCGGDLTGPSGVILSPNYPEPYPPGKECDWKVTVSPDYVIALVFNIFNLEPGYDFLHI
YDGRDSLSPLIGSFYGSQLPGRIESSSNSLFLAFRSDASVSNAGFVIDYTENPRESCFDPGSIKNGTRVG
SDLKLGSSVTYYCHGGYEVEGTSTLSCILGPDGKPVWNNPRPVCTAPCGGQYVGSDGVVLSPNYPQNYTS
GQICLYFVTVPKDYVVFGQFAFFHTALNDVVEVHDGHSQHSRLLSSLSGSHTGESLPLATSNQVLIKFSA
KGLAPARGFHFVYQAVPRTSATQCSSVPEPRYGKRLGSDFSVGAIVRFECNSGYALQGSPEIECLPVPGA
LAQWNVSAPTCVVPCGGNLTERRGTILSPGFPEPYLNSLNCVWKIVVPEGAGIQIQVVSFVTEQNWDSLE
VFDGADNTVTMLGSFSGTTVPALLNSTSNQLYLHFYSDISVSAAGFHLEYKTVGLSSCPEPAVPSNGVKT
GERYLVNDVVSFQCEPGYALQGHAHISCMPGTVRRWNYPPPLCIAQCGGTVEEMEGVILSPGFPGNYPSN
MDCSWKIALPVGFGAHIQFLNFSTEPNHDYIEIRNGPYETSRMMGRFSGSELPSSLLSTSHETTVYFHSD
HSQNRPGFKLEYQAYELQECPDPEPFANGIVRGAGYNVGQSVTFECLPGYQLTGHPVLTCQHGTNRNWDH
PLPKCEVPCGGNITSSNGTVYSPGFPSPYSSSQDCVWLITVPIGHGVRLNLSLLQTEPSGDFITIWDGPQ
QTAPRLGVFTRSMAKKTVQSSSNQVLLKFHRDAATGGIFAIAFSAYPLTKCPPPTILPNAEVVTENEEFN
IGDIVRYRCLPGFTLVGNEILTCKLGTYLQFEGPPPICEVHCPTNELLTDSTGVILSQSYPGSYPQFQTC
SWLVRVEPDYNISLTVEYFLSEKQYDEFEIFDGPSGQSPLLKALSGNYSAPLIVTSSSNSVYLRWSSDHA
YNRKGFKIRYSAPYCSLPRAPLHGFILGQTSTQPGGSIHFGCNAGYRLVGHSMAICTRHPQGYHLWSEAI
PLCQALSCGLPEAPKNGMVFGKEYTVGTKAVYSCSEGYHLQAGAEATAECLDTGLWSNRNVPPQCVPVTC
PDVSSISVEHGRWRLIFETQYQFQAQLMLICDPGYYYTGQRVIRCQANGKWSLGDSTPTCRIISCGELPI
PPNGHRIGTLSVYGATAIFSCNSGYTLVGSRVRECMANGLWSGSEVRCLAGHCGTPEPIVNGHINGENYS
YRGSVVYQCNAGFRLIGMSVRICQQDHHWSGKTPFCVPITCGHPGNPVNGLTQGNQFNLNDVVKFVCNPG
YMAEGAARSQCLASGQWSDMLPTCRIINCTDPGHQENSVRQVHASGPHRFSFGTTVSYRCNHGFYLLGTP
VLSCQGDGTWDRPRPQCLLVSCGHPGSPPHSQMSGDSYTVGAVVRYSCIGKRTLVGNSTRMCGLDGHWTG
SLPHCSGTSVGVCGDPGIPAHGIRLGDSFDPGTVMRFSCEAGHVLRGSSERTCQANGSWSGSQPECGVIS
CGNPGTPSNARVVFSDGLVFSSSIVYECREGYYATGLLSRHCSVNGTWTGSDPECLVINCGDPGIPANGL
RLGNDFRYNKTVTYQCVPGYMMESHRVSVLSCTKDRTWNGTKPVCKALMCKPPPLIPNGKVVGSDFMWGS
SVTYACLEGYQLSLPAVFTCEGNGSWTGELPQCFPVFCGDPGVPSRGRREDRGFSYRSSVSFSCHPPLVL
VGSPRRFCQSDGTWSGTQPSCIDPTLTTCADPGVPQFGIQNNSQGYQVGSTVLFRCQKGYLLQGSTTRTC
LPNLTWSGTPPDCVPHHCRQPETPTHANVGALDLPSMGYTLITPARRASPSRVAPSTAPARRMAAGQASR
PSAWRSGPVGDPSTLPGSHRSPKP

A search of sequence databases reveals that the NOV1a amino acid sequence has 145 of 489 amino acid residues (29%) identical to, and 216 of 489 amino acid residues (44%) similar to, the 2489 amino acid residue ptnr:SPTREMBL-ACC:Q16744 protein from Homo sapiens (Human) (COMPLEMENT RECEPTOR 1). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

NOV1 is expressed in at least the adrenal gland and the pituitary gland. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

NOV1b

A disclosed NOV1b nucleic acid of 8010 nucleotides (also referred to as CG50377-02) encoding a cub and sushi domain-containing protein-like protein is shown in Table 1C.

Table 1C. NOV1b nucleotide sequence (SEQ ID NO:3).

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ATGGCGGGCGCCCCTCCCCCCGCCTTGCTGCTGCCTTGCAGTTTGATCTCAGACTGCTGT
GCTAGCAATCAGCGACACTCCGTGGGCGTAGGACCCTCCGAGCTAGTCAAGAAGCAAATT
GAGTTGAAGTCTCGAGGTGTGAAGCTGATGCCCAGCAAAGACAACAGCCAGAAGACGTCT
GTGTTAACTCAGGTTGGTGTGTCCCAAGGACATAATATGTGTCCAGACCCTGGCATACCC
GAAAGGGGCAAAAGACTAGGCTCGGATTTCAGGTTAGGATCCAGCGTCCAGTTCACCTGC
AACGAGGGCTATGACCTGCAAGGGTCCAAGCGGATCACCTGTATGAAAGTGAGCGACATG
TTTGCGGCCTGGAGCGACCACAGGCCAGTCTGCCGAGCCCGCATGTGTGATGCCCACCTT
CGAGGCCCCTCGGGCATCATCACCTCCCCCAATTTCCCCATTCAGTATGACAACAATGCA
CACTGTGTGTGGATCATCACAGCACTCAACCCCTCCAAGGTGATCAAGCTCGCCTTTGAG
GAGTTTGATTTGGAGAGGGGCTATGACACCCTGACGGTCGGTGATGGTGGTCAGGATGGG
GACCAGAAGACAGTTCTCTACATGTCTCAAAATGCCTGCAGTGACAGCCCTCACACCCCA
GGCTCTCGCATCCCAGAGAGCATGTCTGGGGACATCTGGAGGCAGAAATGGACTGTACTT
GAGATCTGTCGTGACATTAGCAGTTCAGATGCAAGGTCAGGTTCAGTGAGGAAGTCTCCA
AAGACTTCTAATGCTGTGGAACTTGTTGCTCCTGGGACAGAGATCGAGCAGGGCAGTTGC
GGTGACCCTGGCATACCTGCATATGGCCGGAGGGAAGGCTCCCGGTTTCACCACGGTGAC
ACACTCAAGTTTGAGTGCCAGCCCGCCTTTGAGCTGGTGGGACAGAAGGCAATCACATGC
CAAAAGAATAACCAATGGTCGGCTAAGAAGCCAGGCTGCGTGTTCTCCTGCTTCTTCAAC
TTCACCAGCCCGTCTGGGGTTGTCCTGTCTCCCAACTACCCAGAGGACTATGGCAACCAC
CTCCACTGTGTCTGGCTCATCCTGGCCAGGCCTGAGAGCCGCATCCACCTGGCCTTCAAC
GACATTGACGTGGAGCCTCAGTTTGATTTCCTGGTCATCAAGGATGGGGCCACCGCCGAG
GCGCCCGTCCTGGGCACCTTCTCAGGAAACCAGCTTCCCTCCTCCATCACAAGCAGTGGC
CACGTGGCCCGTCTCGAGTTCCAGACTGACCACTCCACAGGGAAGAGGGGCTTCAACATC
ACTTTTACCACCTTCCGACACAACGAGTGCCCGGATCCTGGCGTTCCAGTAAATGGCAAA
CGGTTTGGGGACAGCCTCCAGCTGGGCAGCTCCATCTCCTTCCTCTGTGATGAAGGCTTC
CTTGGGACTCAGGGCTCAGAGACCATCACCTGCGTCCTGAAGGAGGGCAGCGTGGTCTGG
AACAGCGCTGTGCTGCGGTGTGAAGCTCCCTGTGGTGGTCACCTGACTTCGCCCAGCGGC
ACCATCCTCTCTCCGGGCTGGCCTGGCTTCTACAAGGATGCCTTGAGCTGTGCCTGGGTG
ATTGAGGCCCAGCCAGGCTACCCCATCAAAATCACCTTCGACAGATTCAAAACCGAGGTC
AACTATGACACCCTGGAAGTACGCGATGGGCGGACTTACTCAGCGCCCTTGATCGGGGTT
TACCACGGGACCCAGGTTCCCCAGTTCCTCATCAGCACCAGCAACTACCTCTACCTCCTC
TTCTCTACCGACAAGAGTCACTCGGACATCGGCTTCCAGCTCCGCTATGAGACTATAACA
CTGCAGTCAGACCACTGTCTGGATCCAGGAATCCCAGTAAATGGACAGCGTCATGGGAAT
GACTTCTACGTGGGCGCGCTGGTGACCTTCAGCTGTGACTCGGGCTACACATTAAGTGAC
GGGGAGCCTCTGGAGTGTGAGCCCAACTTCCAGTGGAGCCGGGCCCTGCCCAGTTGTGAA
GCTCTCTGTGGTGGCTTCATTCAAGGCTCCAGTGGGACCATCTTGTCGCCAGGGTTCCCT
GACTTCTACCCCAACAACTTGAACTGCACCTGGATTATCGAAACATCTCATGGCAAGGGT
GTGTTCTTCACTTTCCACACCTTCCACCTGGAAAGTGGCCATGACTACCTCCTCATCACT
GAGAACGGCAGCTTCACCCAGCCCCTGAGGCAGCTAACTGGATCTCGGCTGCCAGCTCCC
ATCAGCGCTGGGCTCTATGGCAACTTCACTGCCCAGGTCCGCTTCATCTCTGATTTCTCC
ATGTCATATGAAGGATTCAACATCACCTTCTCAGAGTACGACTTGGAGCCCTGTGAGGAG
CCCGAGGTCCCAGCCTACAGCATCCGGAAGGGCTTGCAGTTTGGCGTGGGCGACACCTTG
ACCTTCTCCTGCTTCCCCGGGTACCGTCTGGAGGGCACCGCCCGCATCACGTGCCTGGGG
GGCAGACGGCGCCTGTGGAGCTCGCCTCTGCCAAGGTGTGTTGCTGAGTGTGGGAATTCA
GTCACAGGCACTCAGGGTACTTTGCTGTCCCCCAACTTTCCTGTGAACTACAATAACAAT
CATGAATGCATCTACTCCATCCAGACCCAGCCAGGGAAGGGAATTCAGCTGAAAGCCAGG
GCATTCGAACTCTCCGAAGGAGATGTCCTCAAGGTTTATGATGGCAACAACAACTCCGCC
CGTTTGCTGGGAGTTTTTAGCCATTCTGAGATGATGGGGGTGACTTTGAACAGCACATCC
AGCAGTCTGTGGCTTGATTTCATCACTGATGCTGAAAACACCAGCAAGGGCTTTGAACTG
CACTTTTCCAGCTTTGAACTCATCAAATGTGAGGACCCAGGAACCCCCAAGTTTGGCTAC
AAGGTTCATGATGAAGGTCATTTTGCAGGGAGCTCCGTGTCCTTCAGCTGTGACCCTGGA
TACAGCCTGCGGGGTAGTGAGGAGCTGCTGTGTCTGAGTGGAGAGCGCCGGACCTGGGAC
CGGCCTCTGCCCACCTGTGTCGCCGAGTGTGGAGGGACAGTGAGAGGAGAGGTGTCGGGG
CAGGTGCTGTCACCCGGGTATCCAGCTCCCTATGAACACAATCTCAACTGCATCTGGACC
ATCGAAGCAGAGGCCGGCTGCACCATTGGGCTACACTTCCTGGTGTTTGACACAGAGGAG
GTTCACGACGTGCTGCGCATCTGGGATGGGCCTGTGGAGAGCGGGGTTCTGCTGAAGGAG
CTGAGTGGCCCGGCCCTGCCCAAGGACCTGCATAGCACCTTCAACTCGGTCGTCCTGCAG
TTCAGCACTGACTTCTTCACCAGCAAGCAGGGCTTTGCCATTCAATTTTCAGTGTCCACA
GCAACGTCCTGCAATGACCCTGGGATCCCGCAGAATGGGAGTCGGAGTGGTGACAGTTGG
GAAGCCGGCGACTCCACAGTGTTCCAGTGTGACCCTGGCTACGCGCTGCAGGGAAGTGCA
GAGATCAGCTGTGTGAAGATCGAGAACAGGTTCTTCTGGCAGCCCAGCCCGCCAACATGC
ATCGCTCCCTGCGGGGGAGACCTGACAGGACCATCTGGAGTCATCCTCTCACCAAATTAC
CCAGAACCCTACCCGCCAGGCAAGGAGTGTGACTGGAAAGTGACCGTCTCACCAGACTAC
GTCATCGCCCTGGTATTTAACATCTTTAACCTGGAGCCTGGCTATGACTTCCTCCATATC
TACGACGGACGGGACTCTCTCAGCCCTCTCATAGGAAGCTTCTATGGCTCCCAGCTCCCA
GGCCGCATTGAAAGCAGCAGCAACAGCCTCTTCCTCGCCTTCCGCAGCGATGCATCTGTG
AGCAATGCTGGCTTCGTCATTGACTATACAGAAAACCCGCGGGAGTCATGTTTTGATCCT
GGTTCCATCAAGAACGGCACACGGGTGGGGTCCGACCTGAAGCTGGGCTCCTCCGTCACC
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TACTACTGCCACGGGGGCTACGAAGTTGAGGGCACCTCGACCCTGAGCTGCATCCTGGGG
CCTGATGGGAAGCCCGTGTGGAACAATCCCCGGCCAGTCTGCACAGCCCCCTGTGGGGGA
CAGTATGTGGGTTCGGACGGAGTGGTCTTGTCCCCCAACTACCCCCAGAACTACACCAGT
GGACAGATCTGCTTGTATTTTGTTACTGTGCCCAAGGACTATGTGGTGTTTGGCCAGTTC
GCCTTCTTTCACACGGCCCTCAACGACGTGGTGGAGGTTCACGACGGCCACAGCCAGCAC
TCGCGGCTCCTCAGCTCCCTCTCGGGCTCCCATACAGGAGAATCACTGCCCTTGGCCACC
TCCAATCAAGTTCTCATTAAGTTCAGCGCCAAAGGCCTCGCACCAGCCAGAGGCTTCCAC
TTTGTCTACCAAGCGGTTCCTCGAACCAGCGCCACGCAGTGCAGCTCTGTGCCGGAACCC
CGCTATGGCAAGAGGCTGGGCAGTGACTTCTCGGTGGGGGCCATCGTCCGCTTCGAATGC
AACTCCGGCTATGCCCTGCAGGGGTCGCCAGAGATCGAGTGCCTCCCTGTGCCTGGGGCC
TTGGCCCAATGGAATGTCTCAGCGCCCACGTGTGTGGTGCCGTGTGGAGGCAACCTCACA
GAGCGCAGGGGCACCATCCTGTCCCCTGGCTTCCCAGAGCCGTACCTCAACAGCCTCAAC
TGTGTGTGGAAGATCGTGGTCCCCGAAGGCGCTGGCATCCAGATCCAAGTTGTCAGTTTT
GTGACAGAGCAGAACTGGGACTCGCTGGAAGTATTTGATGGTGCAGATAACACTGTAACC
ATGCTGGGGAGTTTCTCAGGAACAACCGTGCCTGCCCTTCTGAACAGCACCTCCAACCAG
CTCTACCTTCATTTCTACTCAGATATCAGCGTATCTGCAGCTGGCTTCCACTTGGAGTAC
AAAACGGTGGGCCTGAGCAGTTGTCCGGAACCTGCTGTGCCCAGTAACGGGGTGAAGACT
GGCGAGCGCTACTTGGTGAATGATGTGGTGTCTTTCCAGTGTGAGCCGGGATATGCCCTC
CAGGGCCACGCCCACATCTCCTGCATGCCCGGAACAGTGCGGCGATGGAACTACCCTCCT
CCACTCTGTATTGCACAGTGTGGGGGAACAGTGGAGGAGATGGAGGGGGTGATCCTGAGC
CCCGGCTTCCCAGGCAACTACCCCAGTAACATGGACTGCTCCTGGAAAATAGCACTGCCC
GTGGGCTTTGGAGCTCACATCCAGTTCCTGAACTTCTCCACCGAGCCCAACCACGACTAC
ATAGAAATCCGGAATGGCCCCTATGAGACCAGCCGCATGATGGGAAGATTCAGTGGAAGC
GAGCTTCCAAGCTCCCTCCTCTCCACGTCCCACGAGACCACCGTGTATTTCCACAGCGAC
CACTCCCAGAATCGGCCAGGATTCAAGCTGGAGTATCAGGCCTATGAACTTCAAGAGTGC
CCAGACCCAGAGCCCTTTGCCAATGGCATTGTGAGGGGAGCTGGCTACAACGTGGGACAA
TCAGTGACCTTCGAGTGCCTCCCGGGGTATCAATTGACTGGCCACCCTGTCCTCACGTGT
CAACATGGCACCAACCGGAACTGGGACCACCCCCTGCCCAAGTGTGAAGTCCCTTGTGGC
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CTCAGCCTGCTGCAGACAGAGCCCTCTGGAGATTTCATCACCATCTGGGATGGGCCACAG
CAAACAGCACCACGGCTCGGCGTCTTCACCCGGAGCATGGCCAAGAAAACAGTGCAGAGT
TCATCCAACCAGGTCCTGCTCAAGTTCCACCGTGATGCAGCCACAGGGGGGATCTTCGCC
ATAGCTTTCTCCGCTTATCCACTCACCAAATGCCCTCCTCCCACCATCCTCCCCAACGCC
GAAGTCGTCACAGAGAATGAAGAATTCAATATAGGTGACATCGTACGCTACAGATGCCTC
CCTGGCTTTACCTTAGTGGGGAATGAAATTCTGACCTGCAAACTTGGAACCTACCTGCAG
TTTGAAGGACCACCCCCGATATGTGAAGTGCACTGTCCAACAAATGAGCTTCTGACAGAC
TCCACAGGCGTGATCCTGAGCCAGAGCTACCCTGGAAGCTATCCCCAGTTCCAGACCTGC
TCTTGGCTGGTGAGAGTGGAGCCCGACTATAACATCTCCCTCACAGTGGAGTACTTCCTC
AGCGAGAAGCAATATGATGAGTTTGAGATTTTTGATGGTCCATCAGGACAGAGTCCTCTG
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GTGTACCTGCGTTGGTCATCTGATCACGCCTACAATCGGAAGGGCTTCAAGATCCGCTAT
TCAGCCCCTTACTGCAGCCTGCCCAGGGCTCCACTCCATGGCTTCATCCTAGGCCAGACC
AGCACCCAGCCCGGGGGCTCCATCCACTTTGGCTGCAACGCCGGCTACCGCCTGGTGGGA
CACAGCATGGCCATCTGTACCCGGCACCCCCAGGGCTACCACCTGTGGAGCGAAGCCATC
CCTCTCTGTCAAGCTCTTTCCTGTGGGCTTCCTGAGGCCCCCAAGAATGGAATGGTGTTT
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CAGGCAGGCGCTGAGGCCACTGCAGAGTGTCTGGACACAGGCCTATGGAGCAACCGCAAT
GTCCCACCACAGTGTGTCCGTGAGTCCTCGGGCAATGGAGGCGGGTCTGTGACTTGTCCT
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CAGTTCCAGGCCCAGCTGATGCTCATCTGTGACCCTGGCTACTACTATACTGGCCAAAGG
GTCATCCGCTGTCAGGCCAATGGCAAATGGAGCCTCGGGGACTCTACGCCCACCTGCCGA
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CTCACCAAAGCTGGACACTGTGGGACTCCTGAGCCCATTGTCAACGGACACATCAATGGG
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GTCCACGCCAGCGGCCCGCACAGGTTCAGCTTCGGCACCACTGTGTCTTACCGGTGCAAC
CACGGCTTCTACCTCCTGGGCACCCCAGTGCTCAGCTGCCAGGGAGATGGCACATGGGAC
CGTCCCCGCCCCCAGTGTCTCTGTAAGTAG

The disclosed NOV1b polypeptide (SEQ ID NO:4) encoded by SEQ ID NO:3 has 2669 amino acid residues and is presented in Table 1D using the one-letter amino acid code.

Table 1D. Encoded NOV1b protein sequence (SEQ ID NO:4).

```
MAGAPPPALLLPCSLISDCCASNQRHSVGVGPSELVKKQIELKSRGVKLMPSKDNSQKTS
 VLTQVGVSQGHNMCPDPGIPERGKRLGSDFRLGSSVQFTCNEGYDLQGSKRITCMKVSDM
 FAAWSDHRPVCRARMCDAHLRGPSGIITSPNFPIQYDNNAHCVWIITALNPSKVIKLAFE
 EFDLERGYDTLTVGDGGQDGDQKTVLYMSQNACSDSPHTPGSRIPESMSGDIWRQKWTVL
 EICRDISSSDARSGSVRKSPKTSNAVELVAPGTEIEQGSCGDPGIPAYGRREGSRFHHGD
 TLKFECQPAFELVGQKAITCQKNNQWSAKKPGCVFSCFFNFTSPSGVVLSPNYPEDYGNH
 LHCVWLILARPESRIHLAFNDIDVEPQFDFLVIKDGATAEAPVLGTFSGNQLPSSITSSG
 HVARLEFQTDHSTGKRGFNITFTTFRHNECPDPGVPVNGKRFGDSLQLGSSISFLCDEGF
 LGTQGSETITCVLKEGSVVWNSAVLRCEAPCGGHLTSPSGTILSPGWPGFYKDALSCAWV
 IEAQPGYPIKITFDRFKTEVNYDTLEVRDGRTYSAPLIGVYHGTQVPQFLISTSNYLYLL
 FSTDKSHSDIGFQLRYETITLQSDHCLDPGIPVNGQRHGNDFYVGALVTFSCDSGYTLSD
 GEPLECEPNFQWSRALPSCEALCGGFIQGSSGTILSPGFPDFYPNNLNCTWIIETSHGKG
 VFFTFHTFHLESGHDYLLITENGSFTQPLRQLTGSRLPAPISAGLYGNFTAQVRFISDFS
 MSYEGFNITFSEYDLEPCEEPEVPAYSIRKGLQFGVGDTLTFSCFPGYRLEGTARITCLG
 GRRRLWSSPLPRCVAECGNSVTGTQGTLLSPNFPVNYNNNHECIYSIQTQPGKGIQLKAR
 AFELSEGDVLKVYDGNNNSARLLGVFSHSEMMGVTLNSTSSSLWLDFITDAENTSKGFEL
 HFSSFELIKCEDPGTPKFGYKVHDEGHFAGSSVSFSCDPGYSLRGSEELLCLSGERRTWD
 RPLPTCVAECGGTVRGEVSGQVLSPGYPAPYEHNLNCIWTIEAEAGCTIGLHFLVFDTEE
 VHDVLRIWDGPVESGVLLKELSGPALPKDLHSTFNSVVLQFSTDFFTSKQGFAIQFSVST
 ATSCNDPGIPQNGSRSGDSWEAGDSTVFQCDPGYALQGSAEISCVKIENRFFWQPSPPTC
 IAPCGGDLTGPSGVILSPNYPEPYPPGKECDWKVTVSPDYVIALVFNIFNLEPGYDFLHI
 YDGRDSLSPLIGSFYGSQLPGRIESSSNSLFLAFRSDASVSNAGFVIDYTENPRESCFDP
 GSIKNGTRVGSDLKLGSSVTYYCHGGYEVEGTSTLSCILGPDGKPVWNNPRPVCTAPCGG
 QYVGSDGVVLSPNYPQNYTSGQICLYFVTVPKDYVVFGQFAFFHTALNDVVEVHDGHSQH
 SRLLSSLSGSHTGESLPLATSNQVLIKFSAKGLAPARGFHFVYQAVPRTSATQCSSVPEP
 RYGKRLGSDFSVGAIVRFECNSGYALQGSPEIECLPVPGALAQWNVSAPTCVVPCGGNLT
 ERRGTILSPGFPEPYLNSLNCVWKIVVPEGAGIQIQVVSFVTEQNWDSLEVFDGADNTVT
 MLGSFSGTTVPALLNSTSNQLYLHFYSDISVSAAGFHLEYKTVGLSSCPEPAVPSNGVKT
 GERYLVNDVVSFQCEPGYALQGHAHISCMPGTVRRWNYPPPLCIAQCGGTVEEMEGVILS
 PGFPGNYPSNMDCSWKIALPVGFGAHIQFLNFSTEPNHDYIEIRNGPYETSRMMGRFSGS
 ELPSSLLSTSHETTVYFHSDHSQNRPGFKLEYQAYELQECPDPEPFANGIVRGAGYNVGQ
 SVTFECLPGYQLTGHPVLTCQHGTNRNWDHPLPKCEVPCGGNITSSNGTVYSPGFPSPYS
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 SSNQVLLKFHRDAATGGIFAIAFSAYPLTKCPPPTILPNAEVVTENEEFNIGDIVRYRCL
 PGFTLVGNEILTCKLGTYLQFEGPPPICEVHCPTNELLTDSTGVILSQSYPGSYPQFQTC
 SWLVRVEPDYNISLTVEYFLSEKQYDEFEIFDGPSGQSPLLKALSGNYSAPLIVTSSSNS
 VYLRWSSDHAYNRKGFKIRYSAPYCSLPRAPLHGFILGQTSTQPGGSIHFGCNAGYRLVG
 HSMAICTRHPQGYHLWSEAIPLCQALSCGLPEAPKNGMVFGKEYTVGTKAMYSCSEGYHL
 QAGAEATAECLDTGLWSNRNVPPQCVRESSGNGGGSVTCPDVSSISVEHGRWRLIFETQY
 QFQAQLMLICDPGYYYTGQRVIRCQANGKWSLGDSTPTCRIISCGELPIPPNGHRIGTLS
 VYGATAIFSCNSGYTLVGSRVRECMANGLWSGSEVRCLATQTKLHSIFYKLLFDVLSSPS
 LTKAGHCGTPEPIVNGHINGENYSYRGSVVYQCNAGFRLIGMSVRICQQDHHWSGKTPFC
 VHVKQQLLLLLLLLCDDDDDEDDGSGAITCGHPGNPVNGLTQGNQFNLNDVVKFVCNPGY
 MAEGAARSQCLASGQWSDMLPTCRIINCTDPGHQENSVRQVHASGPHRFSFGTTVSYRCN
 HGFYLLGTPVLSCQGDGTWDRPRPQCLCK
```

Homologies to either of the above NOV1 proteins will be shared by the other NOV1 protein insofar as they are homologous to each other as shown below. Any reference to NOV1 is assumed to refer to both of the NOV1 proteins in general, unless otherwise noted.

The disclosed NOV1a polypeptide has homology to the amino acid sequences shown in the BLASTP data listed in Table 1E.

Table 1E. BLAST results for NOV1a					
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|16716457|ref|NP_444401.1| (NM_053171)	CUB and Sushi multiple domains 1 [Mus musculus]	3554	54	79	0.0
>gi|15100168|ref|NP_150094.1| (NM_033225)	CUB and Sushi multiple domains 1 [Homo sapiens]	3508	31	45	0.0
gi|14787181|gb|AAG52948.1| (AY017307)	CUB and sushi multiple domains protein 1 short form [Homo sapiens]	3389	31	46	0.0
gi|16162671|ref|XP_053758.2| (XM_053758)	hypothetical protein XP_053758 [Homo sapiens]	1043	70	84	0.0
gi|15620839|dbj|BAB67783.1| (AB067477)	KIAA1890 protein [Homo sapiens]	1048	70	84	0.0

The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 1F. In the ClustalW alignment of the NOV1 proteins, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties), whereas non-highlighted amino acid residues are less conserved and can potentially be altered to a much broader extent without altering protein structure or function.

Table 1F. ClustalW Analysis of NOV1

```
1)  Novel NOV1a  (SEQ ID NO:2)
2)  Novel NOV1b  (SEQ ID NO:4)
3) gi|16716457 (SEQ ID NO: 45)
4) gi|15100168 (SEQ ID NO: 46)
5) gi|14787181 (SEQ ID NO: 47)
6) gi|16162671 (SEQ ID NO: 48)
7) gi|15620839 (SEQ ID NO: 49)

                                10        20        30        40        50
                     ....|....|....|.. .|....|....|....|....|....|....|
NOV1A                ----------------------------------------------------
NOV1B                ---------------------- -----------------------------
gi|16716457|         MTAWRKFKSLLLPLVLAVLCAGLLTAAKGQNCGGLVQGPNGTIESPGFPH
gi|15100168|         MTAWRRFQSLLLLLGLLVLCARLLTAAKGQNCGGLVQGPNGTIESPGFPH
gi|14787181|         MTAWRRFQSLLLLLGLLVLCARLLTAAKGQNCGGLVQGPNGTIESPGFPH
gi|16162671|         ---------------- ---------------------------------
gi|15620839|         ----------------------------------------------------

                                60        70        80        90        100
                     ....|....|....|... .|....|....|....|....|....|....|
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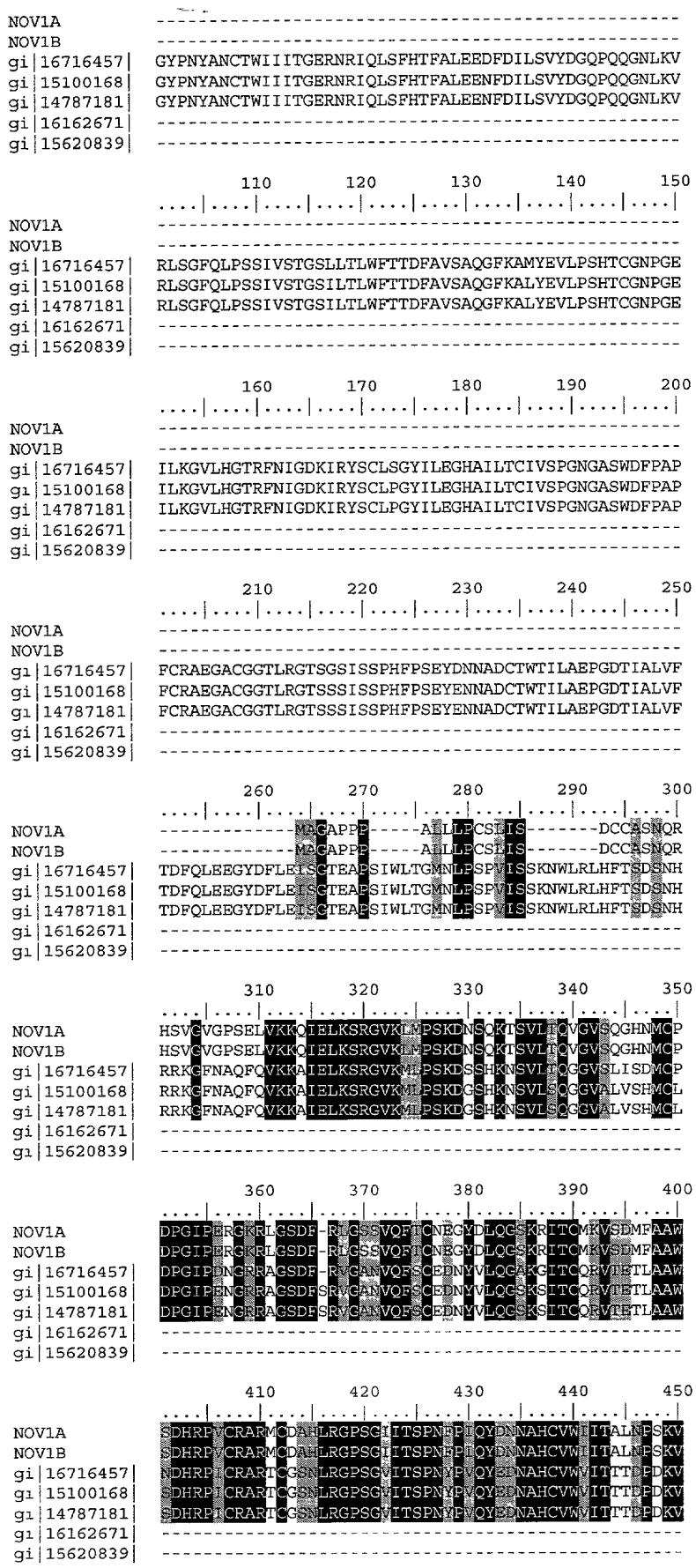
NOV1A
NOV1B
gi|16716457|
gi|15100168|
gi|14787181|
gi|16162671|
gi|15620839|
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GYPNYANCTWIIITGERNRIQLSFHTFALEENFDILSVYDGQPQQGNLKV
GYPNYANCTWIIITGERNRIQLSFHTFALEENFDILSVYDGQPQQGNLKV
110 120 130 140 150
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RLSGFQLPSSIVSTGSILTLWFTTDFAVSAQGFKALYEVLPSHTCGNPGE
RLSGFQLPSSIVSTGSILTLWFTTDFAVSAQGFKALYEVLPSHTCGNPGE
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ILKGVLHGTRFNIGDKIRYSCLSGYILEGHAILTCIVSPGNGASWDFPAP
ILKGVLHGTRFNIGDKIRYSCLPGYILEGHAILTCIVSPGNGASWDFPAP
ILKGVLHGTRFNIGDKIRYSCLPGYILEGHAILTCIVSPGNGASWDFPAP
210 220 230 240 250
FCRAEGACGGTLRGTSGSISSPHFPSEYDNNADCTWTILAEPGDTIALVF
FCRAEGACGGTLRGTSSSISSPHFPSEYENNADCTWTILAEPGDTIALVF
FCRAEGACGGTLRGTSSSISSPHFPSEYENNADCTWTILAEPGDTIALVF
260 270 280 290 300
NOV1A ----------MQCAPPP-----AILLPCSLIS-------DCCASNQR
NOV1B ----------MQCAPPP-----AILLPCSLIS-------DCCASNQR
TDFQLEEGYDFLEISGTEAPSIWLTGMNLPSPVISSKNWLRLHFTSDSNH
TDFQLEEGYDFLEISGTEAPSIWLTGMNLPSPVISSKNWLRLHFTSDSNH
TDFQLEEGYDFLEISGTEAPSIWLTGMNLPSPVISSKNWLRLHFTSDSNH
310 320 330 340 350
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HSVGVGPSELVKKQIELKSRGVKLMPSKDNSQKTSVLTQVGVSQGHNMCP
RRKGFNAQFQVKKAIELKSRGVKMLPSKDSSHKNSVLTQGGVSLISDMCP
RRKGFNAQFQVKKAIELKSRGVKMLPSKDGSHKNSVLSQGGVALVSHMCL
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360 370 380 390 400
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DPGIPENGRRAGSDFSRVGANVQFSCEDNYVLQGSKSITCQRVETLAAW
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SDHRPICRARTCGSNLRGPSGVITSPNYPVQYEDNAHCVWVITTTDPDKV

```
                 460       470       480       490       500
             ....|....|....|....|....|....|....|....|....|....|
NOV1A        IKLAFEEFDLERGYDTLTVGDGGQDGDQKTVLYMSQNACSDSPHTPGSRI
NOV1B        IKLAFEEFDLERGYDTLTVGDGGQDGDQKTVLYMSQNACSDSPHTPGSRI
gi|16716457| IKLAFEEFELERGYDTLTVGDAGKVGDTRSVLYVLT----------GSSV
gi|15100168| IKLAFEEFELERGYDTLTVGDAGKVGDTRSVLYVLT----------GSSV
gi|14787181| IKLAFEEFELERGYDTLTVGDAGKVGDTRSVLYVLT----------GSSV
gi|16162671| --------------------------------------------------
gi|15620839| --------------------------------------------------

                 510       520       530       540       550
             ....|....|....|....|....|....|....|....|....|....|
NOV1A        PESMSGDIWRQKWTVLEICRDISSSDARSGSVRKSPKTSNAVELVAPGTE
NOV1B        PESMSGDIWRQKWTVLEICRDISSSDARSGSVRKSPKTSNAVELVAPGTE
gi|16716457| PDLIV-SMSNQMWLHLQSDDSIGSPGFK-----------------AVYQE
gi|15100168| PDLIV-SMSNQMWLHLQSDDSIGSPGFK-----------------AVYQE
gi|14787181| PDLIV-SMSNQMWLHLQSDDSIGSPGFK-----------------AVYQE
gi|16162671| --------------------------------------------------
gi|15620839| --------------------------------------------------

                 560       570       580       590       600
             ....|....|....|....|....|....|....|....|....|....|
NOV1A        IEQGSCGDPGIPAYGRREGSRFHHGDTLKFECQPAFELVGQKAITCQKNN
NOV1B        IEQGSCGDPGIPAYGRREGSRFHHGDTLKFECQPAFELVGQKAITCQKNN
gi|16716457| IEKGGCGDPGIPAYGKRTGSSFLHGDTLTFECQAAFELVGERVITCQKNN
gi|15100168| IEKGGCGDPGIPAYGKRTGSSFLHGDTLTFECPAAFELVGERVITCQQNN
gi|14787181| IEKGGCGDPGIPAYGKRTGSSFLHGDTLTFECPAAFELVGERVITCQQNN
gi|16162671| --------------------------------------------------
gi|15620839| --------------------------------------------------

                 610       620       630       640       650
             ....|....|....|....|....|....|....|....|....|....|
NOV1A        QWSAKKPGCVFSCFFNFTSPSGVVLSPNYPEDYGNHLHCVWLILARPESR
NOV1B        QWSAKKPGCVFSCFFNFTSPSGVVLSPNYPEDYGNHLHCVWLILARPESR
gi|16716457| QWSGNKPSCVFSCFFNFTAPSGIILSPNYPEEYGNNMNCVWLIISEPGSR
gi|15100168| QWSGNKPSCVFSCFFNFTASSGIILSPNYPEEYGNNMNCVWLIISEPGSR
gi|14787181| QWSGNKPSCVFSCFFNFTASSGIILSPNYPEEYGNNMNCVWLIISEPGSR
gi|16162671| --------------------------------------------------
gi|15620839| --------------------------------------------------

                 660       670       680       690       700
             ....|....|....|....|....|....|....|....|....|....|
NOV1A        IHLAFNDIDVEPQFDFLVIKDGATAEAPVLGTFSGNQLPSSITSSGHVAR
NOV1B        IHLAFNDIDVEPQFDFLVIKDGATAEAPVLGTFSGNQLPSSITSSGHVAR
gi|16716457| IHLIFKDFDVEPQFDFLAVKDDGISDITVLGTFSGNEVPAQLASSGHIVR
gi|15100168| IHLIFNDFDVEPQFDFLAVKDNGISDITVLGTFSGNEVPSQLASSGHIVR
gi|14787181| IHLIFNDFDVEPQFDFLAVKDNGISDITVLGTFSGNEVPSQLASSGHIVR
gi|16162671| --------------------------------------------------
gi|15620839| --------------------------------------------------

                 710       720       730       740       750
             ....|....|....|....|....|....|....|....|....|....|
NOV1A        LEFQTDHSTGKRGFNITFTTFRHNECPDPGVPVNGKRFGDSLQLGSSISF
NOV1B        LEFQTDHSTGKRGFNITFTTFRHNECPDPGVPVNGKRFGDSLQLGSSISF
gi|16716457| LEFQSDHSTTGRGFNITYTTFGQNECHDPGIPVNGRRFGDRFLLGSSVSF
gi|15100168| LEFQSDHSTTGRGFNITYTTFGQNECHDPGIPINGRRFGDRFLLGSSVSF
gi|14787181| LEFQSDHSTTGRGFNITYTTFGQNECHDPGIPINGRRFGDRFLLGSSVSF
gi|16162671| --------------------------------------------------
gi|15620839| --------------------------------------------------

                 760       770       780       790       800
             ....|....|....|....|....|....|....|....|....|....|
NOV1A        LCDEGFLGTQGSETITCVLKEGSVVWNSAVLRCEAPCGGHLTSPSGTILS
NOV1B        LCDEGFLGTQGSETITCVLKEGSVVWNSAVLRCEAPCGGHLTSPSGTILS
gi|16716457| HCDDGFVKTQGSESITCILQDGNVVWSSTVPRCEAPCGGHLTASSGVILP
gi|15100168| HCDDGFVKTQGSESITCILQDGNVVWSSTVPRCEAPCGGHLTASSGVILP
gi|14787181| HCDDGFVKTQGSESITCILQDGNVVWSSTVPRCEAPCGGHLTASSGVILP
gi|16162671| --------------------------------------------------
gi|15620839| --------------------------------------------------

                 810       820       830       840       850
             ....|....|....|....|....|....|....|....|....|....|
NOV1A        PGWPGFYKDALSCAWVIEAQPGYPIKITFDRFKTEVNYDTLEVRDGRTYS
NOV1B        PGWPGFYKDALSCAWVIEAQPGYPIKITFDRFKTEVNYDTLEVRDGRTYS
gi|16716457| PGWPGYYKDSLNCEWVIEAKPGHSIKITFDRFQTEVNYDTLEVRDGPTSS
gi|15100168| PGWPGYYKDSLHCEWIIEAKPGHSIKMTFDRFQTEVNYDTLEVRDGPASS
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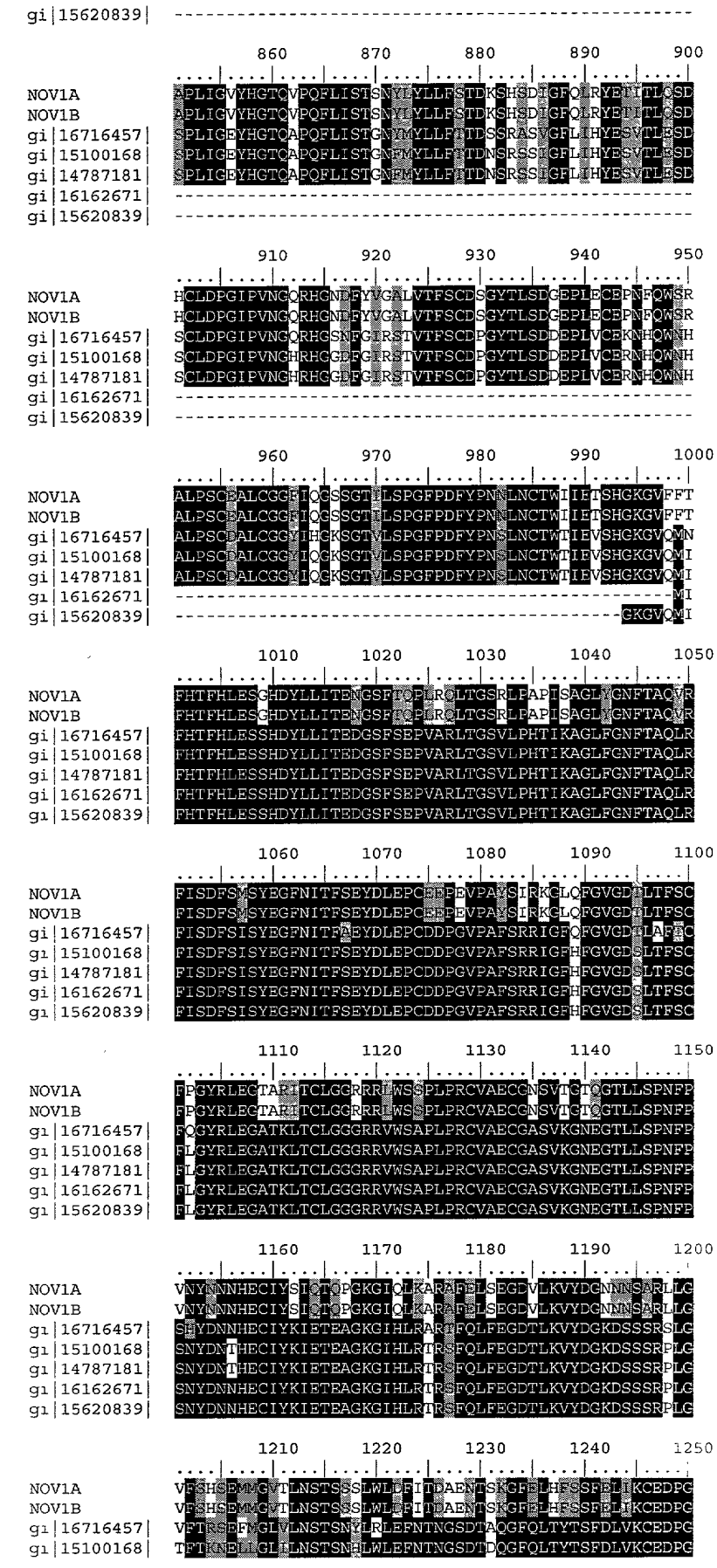
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NOV1B
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NOV1B
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NOV1B
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gi|16162671|
gi|15620839|
1160 1170 1180 1190 1200
NOV1A
NOV1B
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gi|14787181|
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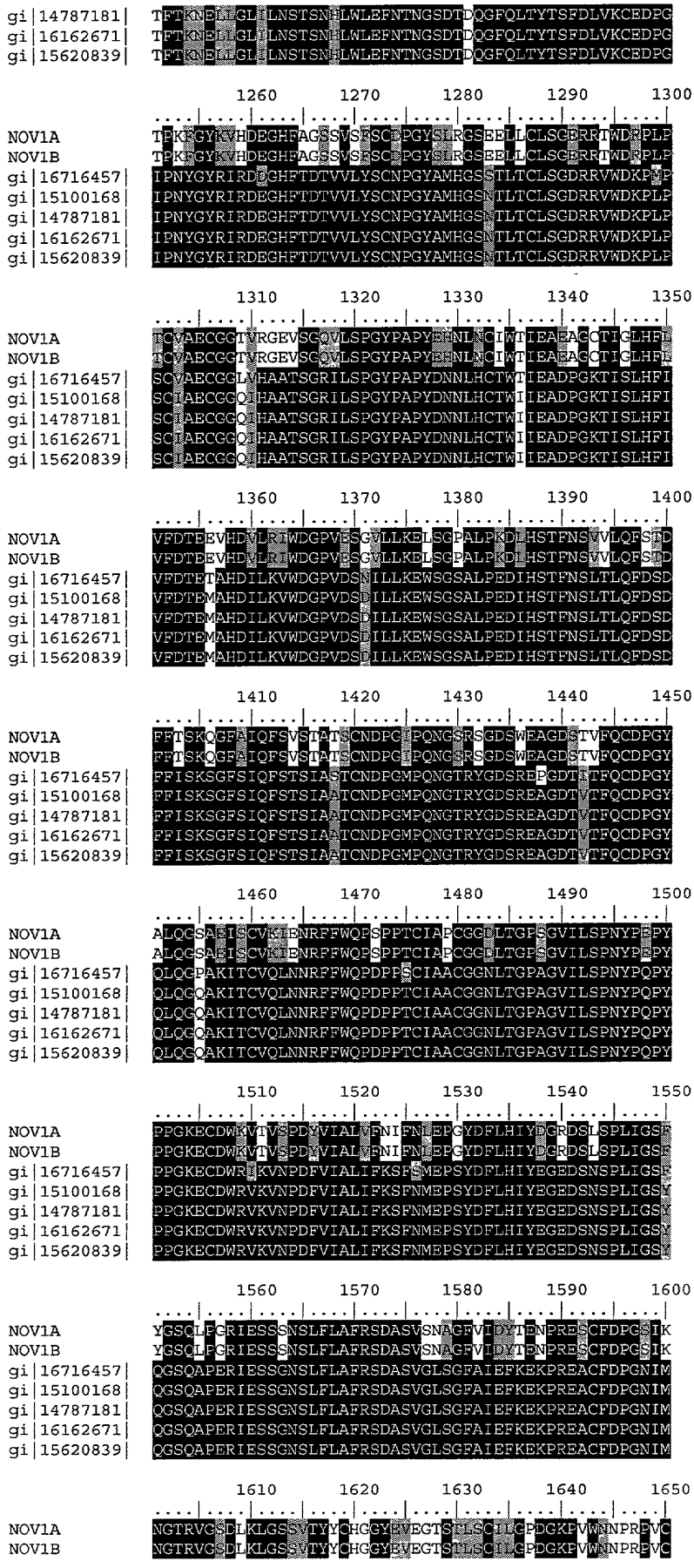
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NOV1B
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NOV1B
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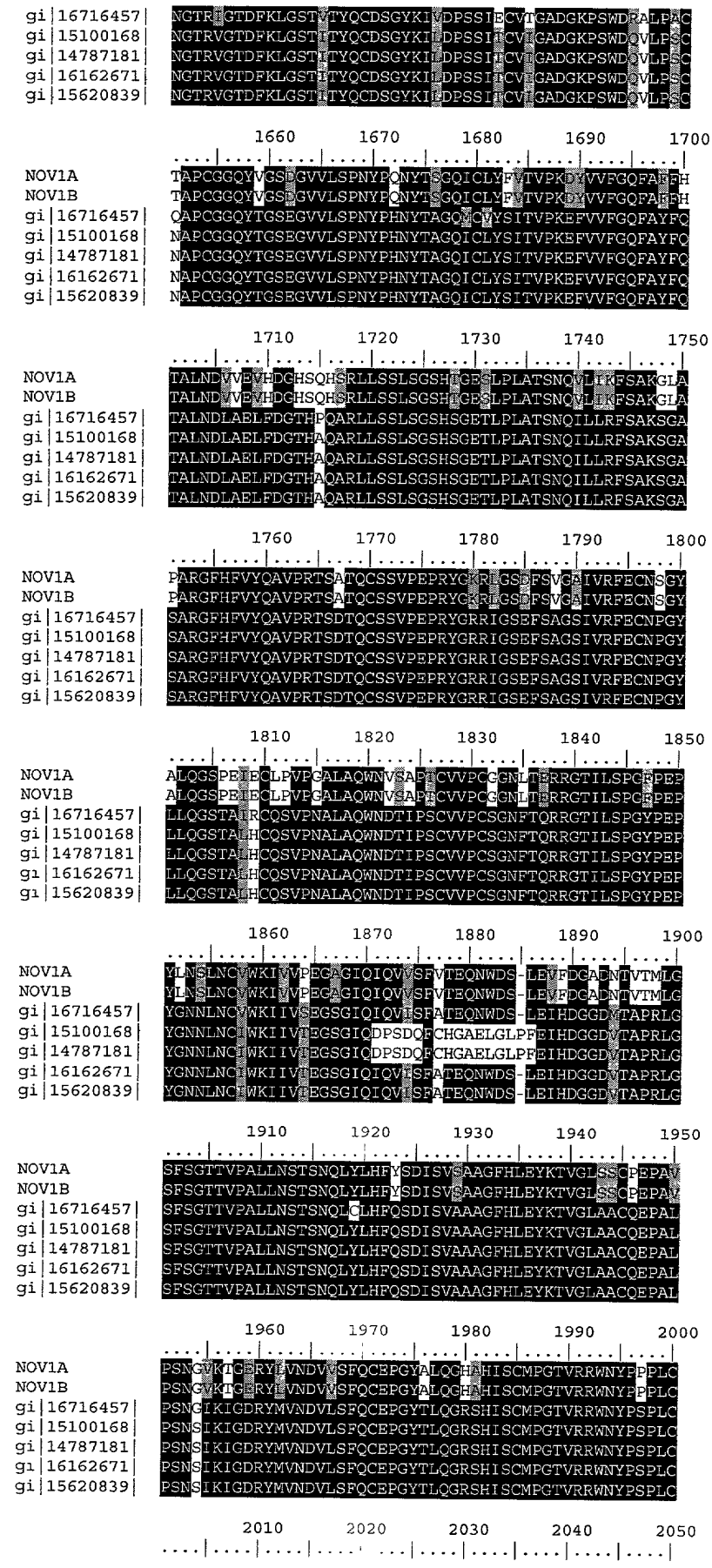
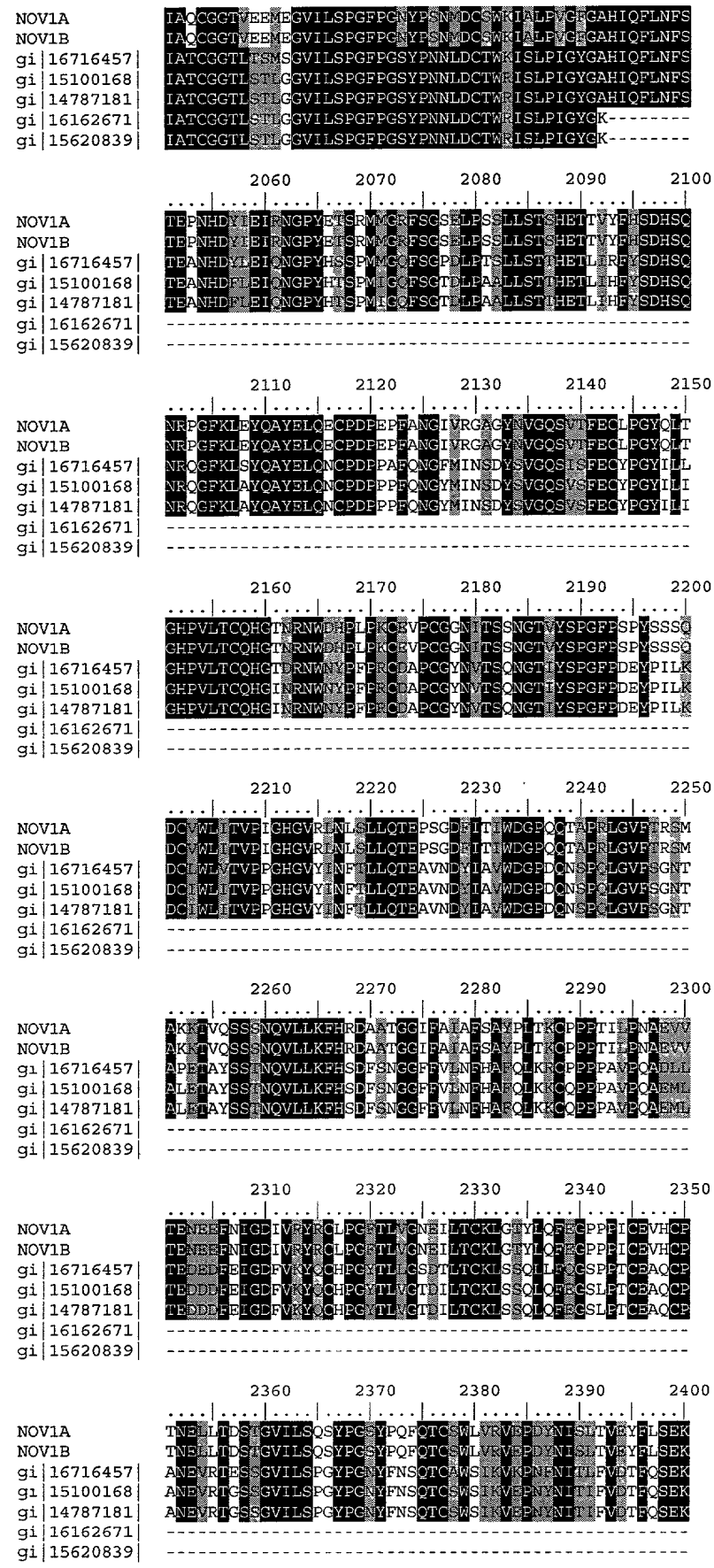
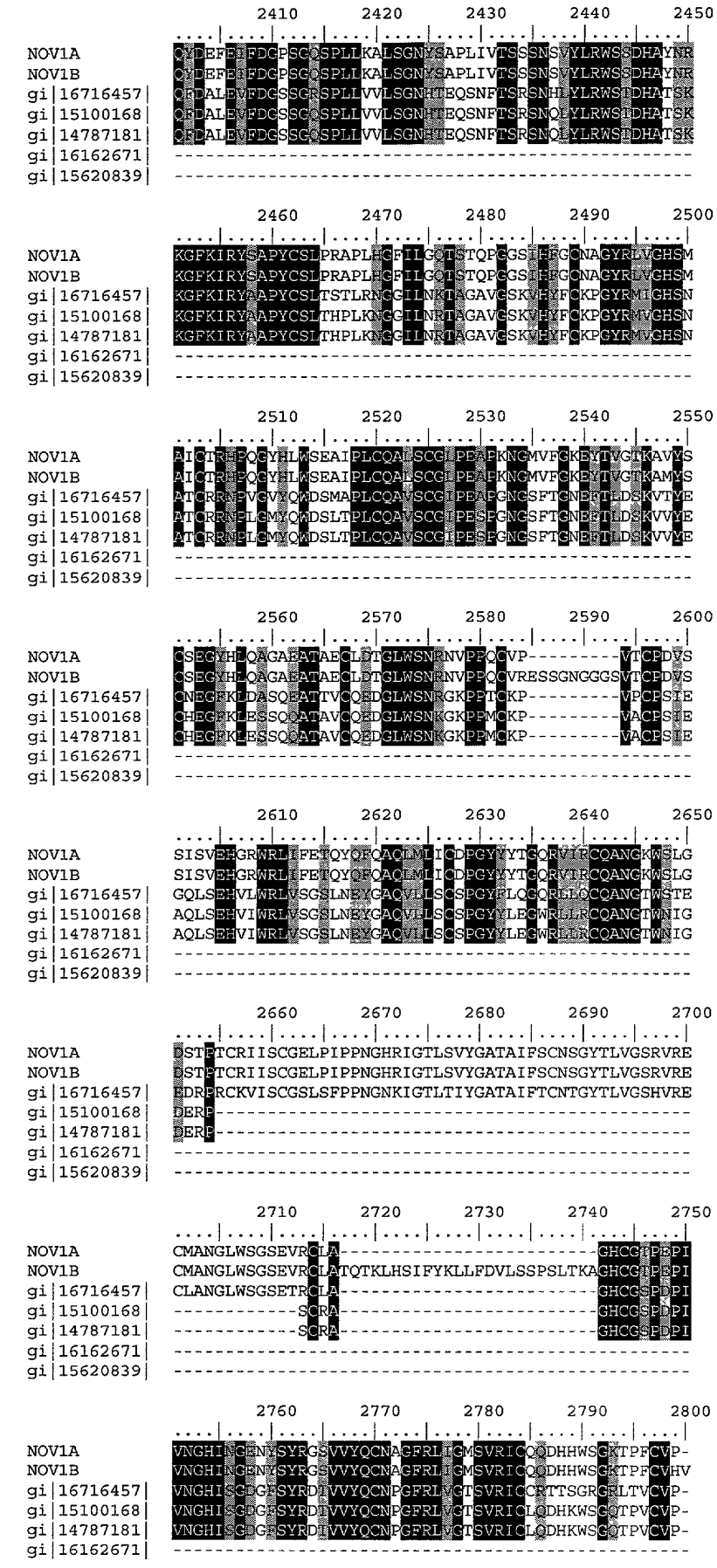
gi|15100168|
gi|14787181|
gi|16162671|
gi|15620839|
1560 1570 1580 1590 1600
NOV1A
NOV1B
gi|16716457|
gi|15100168|
gi|14787181|
gi|16162671|
gi|15620839|
1610 1620 1630 1640 1650
NOV1A
NOV1B






2410 2420 2430 2440 2450
NOV1A
NOV1B
gi|16716457|
gi|15100168|
gi|14787181|
gi|16162671|
gi|15620839|
2460 2470 2480 2490 2500
2510 2520 2530 2540 2550
2560 2570 2580 2590 2600
2610 2620 2630 2640 2650
2660 2670 2680 2690 2700
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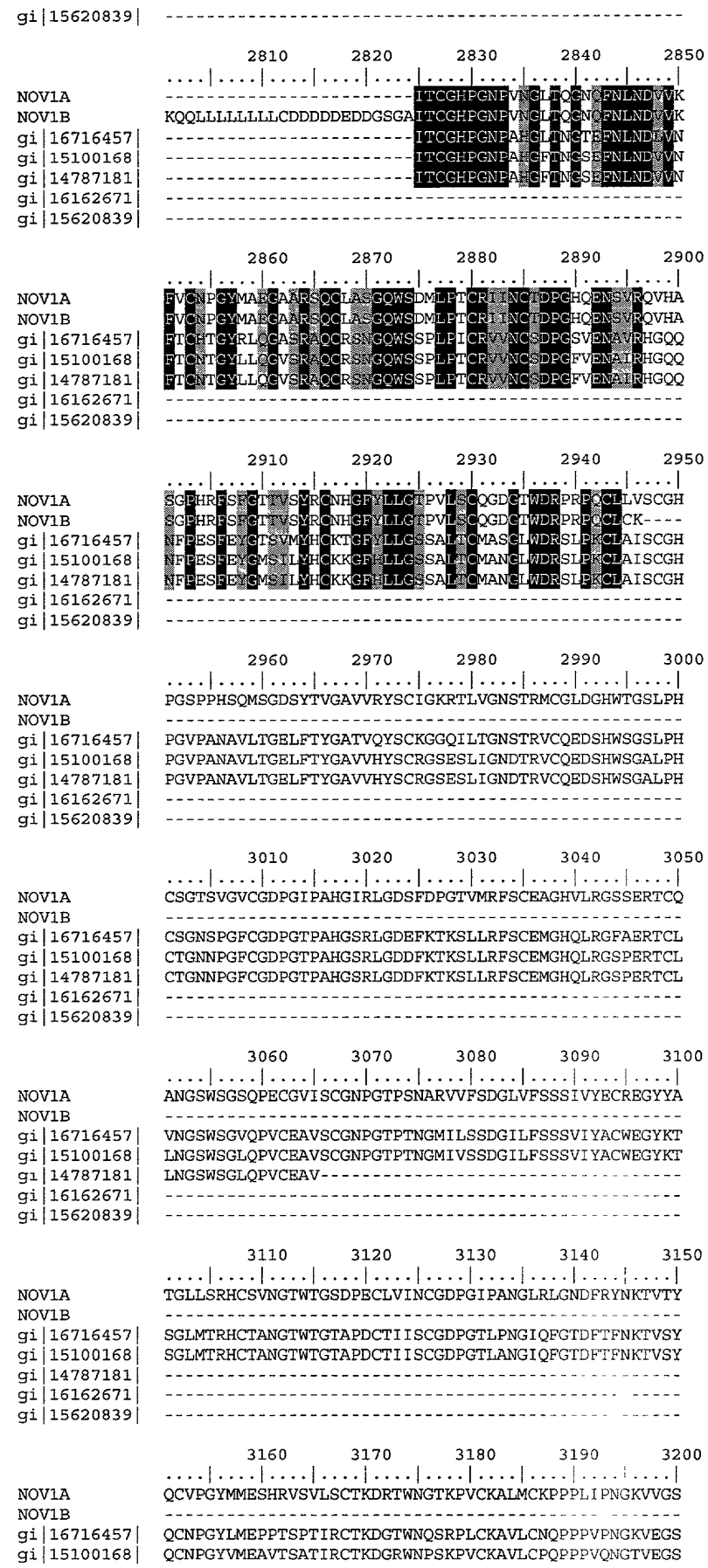
2760 2770 2780 2790 2800



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gi|14787181|  ----------L-----------------------CPQPPPVQNGTVEGS
gi|16162671|  --------------------------------------------------
gi|15620839|  --------------------------------------------------

                       3210      3220      3230      3240      3250
                  ....|....|....|....|....|....|....|....|....|....|
NOV1A             DFMWGSSVTYACLEGYQLSLPAVFTCEGNGSWTGELPQCFPVFCGDPGVP
NOV1B             --------------------------------------------------
gi|16716457|      DFRWGASISYSCVDGYQLSHSAILSCEGRGVWKGEVPQCLPVFCGDPGTP
gi|15100168|      DFRWGSSISYSCMDGYQLSHSAILSCEGRGVWKGEIPQCLPVFCGDPGIP
gi|14787181|      DFRWGSSISYSCMDGYQLSHSAILSCEGRGVWKGEIPQCLPVFCGDPGIP
gi|16162671|      --------------------------------------------------
gi|15620839|      --------------------------------------------------

                       3260      3270      3280      3290      3300
                  ....|....|....|....|....|....|....|....|....|....|
NOV1A             SRGRREDRGFSYRSSVSFSCHPPLVLVGSPRRFCQSDGTWSGTQPSCIDP
NOV1B             --------------------------------------------------
gi|16716457|      AEGRLSGKSFTFKSEVFIQCKPPFVLVGSSRRTCQADGIWSGIQPTCIDP
gi|15100168|      AEGRLSGKSFTYKSEVFFQCKSPFILVGSSRRVCQADGTWSGIQPTCIDP
gi|14787181|      AEGRLSGKSFTYKSEVFFQCKSPFILVGSSRRVCQADGTWSGIQPTCIDP
gi|16162671|      --------------------------------------------------
gi|15620839|      --------------------------------------------------

                       3310      3320      3330      3340      3350
                  ....|....|....|....|....|....|....|....|....|....|
NOV1A             TLTTCADPGVPQFGIQNNSQGYQVGSTVLFRCQKGYLLQGSTTRTCLPNL
NOV1B             --------------------------------------------------
gi|16716457|      AHTACPDPGTPHFGIQNSSKGYEVGSTVFFRCRKGYHIQGSTTRTCLANL
gi|15100168|      AHNTCPDPGTPHFGIQNSSRGYEVGSTVFFRCRKGYHIQGSTTRTCLANL
gi|14787181|      AHNTCPDPGTPHFGIQNSSRGYEVGSTVFFRCRKGYHIQGSTTRTCLANL
gi|16162671|      --------------------------------------------------
gi|15620839|      --------------------------------------------------

                       3360      3370      3380      3390      3400
                  ....|....|....|....|....|....|....|....|....|....|
NOV1A             TWSGTPPDCVPHHCRQPETPTHANVGALDLPSMGYTLITPAR--------
NOV1B             --------------------------------------------------
gi|16716457|      TWSGIQTECIPHACRQPETPAHADVRAIDLPAFGYTLVYTCHPGFFLAGG
gi|15100168|      TWSGIQTECIPHACRQPETPAHADVRAIDLPTFGYTLVYTCHPGFFLAGG
gi|14787181|      TWSGIQTECIPHACRQPETPAHADVRAIDLPTFGYTLVYTCHPGFFLAGG
gi|16162671|      --------------------------------------------------
gi|15620839|      --------------------------------------------------

                       3410      3420      3430      3440      3450
                  ....|....|....|....|....|....|....|....|....|....|
NOV1A             ------------------------RASPSRVAPSTAPARRMAAG------
NOV1B             --------------------------------------------------
gi|16716457|      SEHRTCKADMKWTGKSPVCKSKGVREVNETVTKTPVPSDVFFINSVWKGY
gi|15100168|      SEHRTCKADMKWTGKSPVCKSKGVREVNETVTKTPVPSDVFFVNSLWKGY
gi|14787181|      SEHRTCKADMKWTGKSPVCKSKGVREVNETVTKTPVPSDVFFVNSLWKGY
gi|16162671|      --------------------------------------------------
gi|15620839|      --------------------------------------------------

                       3460      3470      3480      3490      3500
                  ....|....|....|....|....|....|....|....|....|....|
NOV1A             -------------------QASRPSAWRSGPVGDPSTLPGSHRSPKP---
NOV1B             --------------------------------------------------
gi|16716457|      YEYLGKRQPATLTVDWFNATSSKVNATFTAASRVQLELTGVYKKEEAHLL
gi|15100168|      YEYLGKRQPATLTVDWFNATSSKVNATFSEASPVELKLTGIYKKEEAHLL
gi|14787181|      YEYLGKRQPATLTVDWFNATSSKVNATFSEASPVELKLTGIYKKEEAHLL
gi|16162671|      --------------------------------------------------
gi|15620839|      --------------------------------------------------

                       3510      3520      3530      3540      3550
                  ....|....|....|....|....|....|....|....|....|....|
NOV1A             --------------------------------------------------
NOV1B             --------------------------------------------------
gi|16716457|      LKAFHIKGPADIFVSKFENDNWGLDGYVSSGLERGGFSFQGDIHGKDFGK
gi|15100168|      LKAFQIKGQADIFVSKFENDNWGLDGYVSSGLERGGFTFQGDIHGKDFGK
gi|14787181|      LKAFQIKGQADIFVSKFENDNWGLDGYVSSGLERGGFTFQGDIHGKDFGK
gi|16162671|      --------------------------------------------------
gi|15620839|      --------------------------------------------------

                       3560      3570      3580      3590      3600
                  ....|....|....|....|....|....|....|....|....|....|
NOV1A             --------------------------------------------------
NOV1B             --------------------------------------------------
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```
gi|16716457|  FKLERQDPSNSDADSSNHYQGTSSGSVAAAILVPFFALILSGFAFYLYKH
gi|15100168|  FKLERQDPLNPDQDSSSHYHGTSSGSVAAAILVPFFALILSGFAFYLYKH
gi|14787181|  FKLERQDPLNPDQDSSSHYHGTSSGSVAAAILVPFFALILSGFAFYLYKH
gi|16162671|  --------------------------------------------------
gi|15620839|  --------------------------------------------------

                       3610      3620      3630      3640      3650
                  ....|....|....|....|....|....|....|....|....|....|
NOV1A             --------------------------------------------------
NOV1B             --------------------------------------------------
gi|16716457|  RTRPKVQYNGYAGHENSNGQASFENPMYDTNLKPTEAKAVRFDTTLNTVC
gi|15100168|  RTRPKVQYNGYAGHENSNGQASFENPMYDTNLKPTEAKAVRFDTTLNTVC
gi|14787181|  RTRPKVQYNGYAGHENSNGQASFENPMYDTNLKPTEAKAVRFDTTLNTVC
gi|16162671|  --------------------------------------------------
gi|15620839|  --------------------------------------------------

                  ...
NOV1A             ---
NOV1B             ---
gi|16716457|  TVV
gi|15100168|  TVV
gi|14787181|  TVV
gi|16162671|  ---
gi|15620839|  ---
```

The presence of identifiable domains in NOV1, as well as all other NOVX proteins, was determined by searches using software algorithms such as PROSITE, DOMAIN, Blocks, Pfam, ProDomain, and Prints, and then determining the Interpro number by crossing the domain match (or numbers) using the Interpro website (http:www.ebi.ac.uk/ interpro). DOMAIN results for NOV1 as disclosed in Table 1I, were collected from the Conserved Domain Database (CDD) with Reverse Position Specific BLAST analyses. This BLAST analysis software samples domains found in the Smart and Pfam collections. For Table 1I and all successive DOMAIN sequence alignments, fully conserved single residues are indicated by black shading or by the sign (|) and "strong" semi-conserved residues are indicated by grey shading or by the sign (+). The "strong" group of conserved amino acid residues may be any one of the following groups of amino acids: STA, NEQK, NHQK, NDEQ, QHRK, MILV, MILF, HY, FYW.

Table 1G lists the domain description from DOMAIN analysis results against NOV1a. This indicates that the NOV1a sequence has properties similar to those of other proteins known to contain this domain.

Table 1G. Domain Analysis of NOV1a
gnl|Pfam|pfam00431, CUB, CUB domain
CD-Length = 110 residues, 100.0% aligned Score = 120 bits (301), Expect = 1e-27

Table 1H. Domain Analysis of NOV1a
gnl|Pfam|pfam00084, sushi, Sushi domain (SCR repeat)
CD-Length = 56 residues, 100.0% aligned Score = 57.0 bits (136), Expect = 2e-08

CUB domains are important protein interaction domains that occur primarily in secreted protein, including a variety of biologically important growth factors. CUB domains, when coupled to EGF domains, are important for calcium binding. This protein may mediate cell-cell contact, growth, or other important cellular processes.

The Ca2+-dependent interaction between complement serine proteases C1r and C1s is mediated by their alpha regions, encompassing the major part of their N-terminal CUB-EGF-CUB (where EGF is epidermal growth factor) module array. In order to define the boundaries of the C1r domain(s) responsible for Ca2+ binding and Ca2+-dependent interaction with C1s and to assess the contribution of individual modules to these functions, the CUB, EGF, and CUB-EGF fragments were expressed in eucaryotic systems or synthesized chemically. Gel filtration studies, as well as measurements of intrinsic Tyr fluorescence, provided evidence that the CUB-EGF pair adopts a more compact conformation in the presence of Ca2+. Ca2+-dependent interaction of intact C1r with C1s was studied using surface plasmon resonance spectroscopy, yielding KD values of 10.9-29.7 nM. The C1r CUB-EGF pair bound immobilized C1s with a higher KD (1.5-1.8 microM), which decreased to 31.4 nM when CUB-EGF was used as the immobilized ligand and C1s was free. Half-maximal binding was obtained at comparable Ca2+ concentrations ranging from 5 microM with intact C1r to 10-16 microM for C1ralpha and CUB-EGF. The isolated CUB and EGF fragments or a CUB + EGF mixture did not bind C1s. These data demonstrate that the C1r CUB-EGF module pair (residues 1-175) is the minimal segment required for high affinity Ca2+ binding and Ca2+-dependent interaction with C1s and indicate that Ca2+ binding induces a more compact folding of the CUB-EGF pair. (See Thielens et al., J Biol Chem 1999 Apr 2;274(14):9149-59)

The disclosed NOV1 nucleic acid of the invention encoding a cub and sushi domain-containing protein-like protein includes the nucleic acid whose sequence is provided in Table 1A or 1C, or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 1A or1C while still encoding a protein that maintains its a cub and sushi domain-containing protein - like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described,

including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 1% percent of the bases may be so changed.

The disclosed NOV1 protein of the invention includes the a cub and sushi domain-containing protein-like protein whose sequence is provided in Table 1B or 1D. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 1B or 1D while still encoding a protein that maintains its a cub and sushi domain-containing protein-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 71% percent of the residues may be so changed.

The invention further encompasses antibodies and antibody fragments, such as F_{ab} or $(F_{ab})_2$, that bind immunospecifically to any of the proteins of the invention.

The above defined information for this invention suggests that this a cub and sushi domain-containing protein -like protein (NOV1) may function as a member of a "Calgizzarin family". Therefore, the NOV1 nucleic acids and proteins identified here may be useful in potential therapeutic applications implicated in (but not limited to) various pathologies and disorders as indicated below. The potential therapeutic applications for this invention include, but are not limited to: protein therapeutic, small molecule drug target, antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), diagnostic and/or prognostic marker, gene therapy (gene delivery/gene ablation), research tools, tissue regeneration *in vivo* and *in vitro* of all tissues and cell types composing (but not limited to) those defined here.

The NOV1 nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in cancer including but not limited to various pathologies and disorders as indicated below. For example, a cDNA encoding the a cub and sushi domain-containing protein-like protein (NOV1) may be useful in gene therapy, and the a cub and sushi domain-containing protein-like protein (NOV1) may be useful when administered to a subject in need thereof. By way of nonlimiting example, the compositions of the present invention will have efficacy for treatment of patients suffering from cancer, obesity, inflammation,

hypertension, neurological diseases, neuropsychiatric diseases, small stature, obesity, diabetes, hyperlipidemia and other diseases, disorders and conditions of the like. The NOV1 nucleic acid encoding the a cub and sushi domain-containing protein -like protein of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV1 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immuno-specifically to the novel NOV1 substances for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV1 proteins have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV1 epitope is from about amino acids 400 to 450. In other embodiments, a NOV1 epitope is from about amino acids 500 to 600, from about 1000-1100, from about 1500-1600 and 2500-2800. These novel proteins can be used in assay systems for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV2

A disclosed NOV2 nucleic acid of 1464 nucleotides (also referred to as cg-118733234) encoding a novel myelin-like protein is shown in Table 2A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 334-336 and ending with a TGA codon at nucleotides 1071-1073.

Table 2A. NOV2 nucleotide sequence (SEQ ID NO:5).

CAAAACACAAAAAAGAATAAACAAAAGGTTATCCCCCTTGTCTGCCAACCCCCCTCCCCTCCCAAATTTT
CCCTCCTCTCTTTGACCTCTTATTAACCGTCCACCCTTCTTTCCCCTTTAGAATAGTGAACCCCAGTTAC
CACCACTGATTAGTCATAACCGGTATTACCCCTATCTACTCCACTGAAAGTTACCTGGACAAACAAGAAT
CATATCCCAACCGATATTTGTCTGTGACACATCAGGAACCACAAGCTGCACTTCATTAAAAAATTATTTG
CGTATCACGTGTGGCAAACATTCAAATTCTCCTTCAAACAGTTGGAAGAAAACATGTAATACATTCCAGA
GCAAAGATGAATCAAAAAGTATCTTTTTGCTCAGGAAAAGAATTTCTTCATTCAATTACAGCATAATTCA
TTGAAAGGGGAAGTCATGAGTCTCTTATGAGACTTCCTGAACAGTTTATAAATACAACAAGAACATTTAT
TCAATAAATAAGTGGTTCCTAAAGTCTTTACTGATGATCTCCAGGATTGTCCATCGCTATGGTCCAGGCC
AGCTCCACTTTCTCTGACAGGCTTTAGCTGCCAGTGGAATGGGATGTTTCCTGTCTTTAGGTGACTCTTC
TTGTGTCATACAGACTTTCATCAATATGTCTCTTCATAGTCTGAATCCAGGCACTCAGCGCAACGGACAC
AAGCCTCGCCATACACGCCTCTTCCTCCTCCTGATCAGTGTCATCGGAAACCTCAATAGATGACTTCTTA
TAGCCAGACCTGCTCCTCTTCTTCAGCCCAGCAGCCTTCCTCCCCATTCTCACCAGCAGCAGAGCAACCA
CCACGGCTGAGGGCACAAAGACAAGGATGGAAAGAAGGGCCACAGAGGAAAGCATGGTGCCAAAACCCCT
TTCTGTGACTGTTAGCTCTGTCATGGGAATATTATGGTGCACATCTGGGGGATTCTTCACAGCACAGCTG
AATGTCCCATTGTCCTTTATGGTAGGGTTGCTTATACTTATAGATGCATCCCCTTTGTATACATTTCCAA
CCCAGGAAATCCGATCCCGAAATGTGCCTGCTGTGGTTGGGTACTGGAAAGACTGATAATGAAATATTGA
TACTGTGTGGCTGCTGCTGGGAGGGCGATATGTCCAGTCTATAGTAAGCTTGTCAGTGACATCTGAAGTT
GACTTGAAAGTGCATTTCAACTTGATCTTTTCTCCAACATAACCTCGGACATGGGCATCTGCACGAATCT
CCAAGGAAAAGACGATATAAACACCCTGGAAGAACAGGACGCCCAGCAGAGGGAAGAGAGCGCAGCCACG
GCTTCCAGCTGCTCCTCTCTGCTGCATCCCGGCAGCTCTTCAGATGCTTGCACACCTTGTTTACAGCTCC
CGGTAACGACTACAGGTAACACCGGAAGTGACGTCAGAGCAGGAGGCCGAGAGACAACTTAAAT

The disclosed NOV2 nucleic acid sequence, localized to chromsome 11, has has 175 of 283 bases (61%) identical to a gb:GENBANK-ID:AF030455|acc:AF030455.1 mRNA from Homo sapiens (Homo sapiens epithelial V-like antigen precursor (EVA) mRNA, complete cds).

A NOV2 polypeptide (SEQ ID NO:8) encoded by SEQ ID NO:7 has 246 amino acid residues and is presented using the one-letter code in Table 2B. Signal P, Psort and/or Hydropathy results predict that NOV2 contains a signal peptide with the most likely cleavage site between positions 31 and 32 (i.e. VFS-LE). A NOV2 polypeptide is likely to be localized to the endoplasmic reticulum (membrane) with a certainty of 0.6850. In other embodiments, NOV2 may also be localized to the plasma membrane with a certainty of 0.6400, the Golgi body with a certainty of 0.4600, or the endoplasmic reticulum (lumen) with a certainty of 0.1000.

Table 2B. Encoded NOV2 protein sequence (SEQ ID NO:6).

```
MQQRGAAGSRGCALFPLLGVLFFQGVYIVFSLEIRADAHVRGYVGEKIKLKCTFKSTSDVTDKLTIDWTY
RPPSSSHTVSIFHYQSFQYPTTAGTFRDRISWVGNVYKGDASISISNPTIKDNGTFSCAVKNPPDVHHNI
PMTELTVTERGFGTMLSSVALLSILVFVPSAVVVALLLVRMGRKAAGLKKRSRSGYKKSSIEVSDDTDQE
EEEACMARLVSVALSAWIQTMKRHIDESLYDTRRVT
```

The disclosed NOV2 amino acid sequence has 70 of 192 amino acid residues (36%) identical to, and 101 of 192 amino acid residues (52%) similar to, the 248 amino acid residue ptnr:SWISSNEW-ACC:P25189 protein from Homo sapiens (Human) (MYELIN P0 PROTEIN PRECURSOR).

NOV2 is expressed in at least pituitary gland and prostate. This information was derived by determining the tissue sources of the sequences that were included in the invention. SeqCalling sources: Adrenal Gland/Suprarenal gland, Amygdala, Bone, Bone Marrow, Brain, Colon, Coronary Artery, Dermis, Epidermis, Foreskin,Hair Follicles, Heart, Hippocampus, Hypothalamus, Kidney, Liver, Lung, Lymph node, Lymphoid tissue, Mammarygland/Breast, Oesophagus, Ovary, Pancreas, Parathyroid Gland, Peripheral Blood, Pineal Gland, Pituitary Gland, Placenta,Prostate, Retina, Salivary Glands, Small Intestine, Spleen, Stomach, Testis, Thalamus, Thymus, Tonsils, Trachea, UmbilicalVein, Uterus, Whole Organism.

NOV2 also has homology to the amino acid sequences shown in the BLASTP data listed in Table 2C.

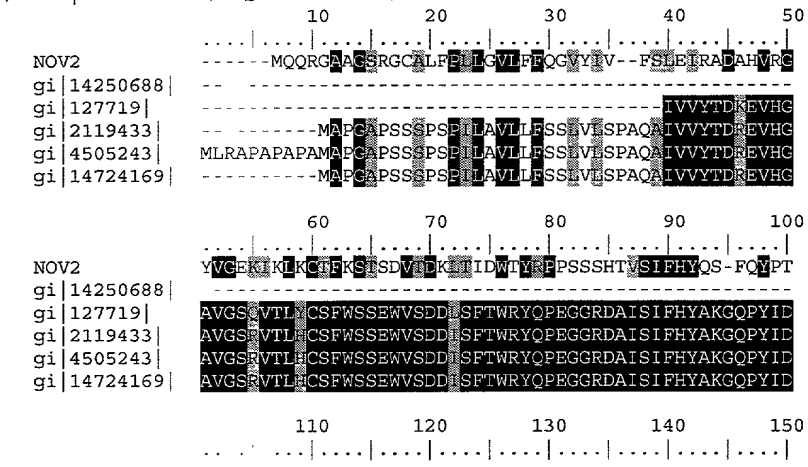
Table 2C. BLAST results for NOV2

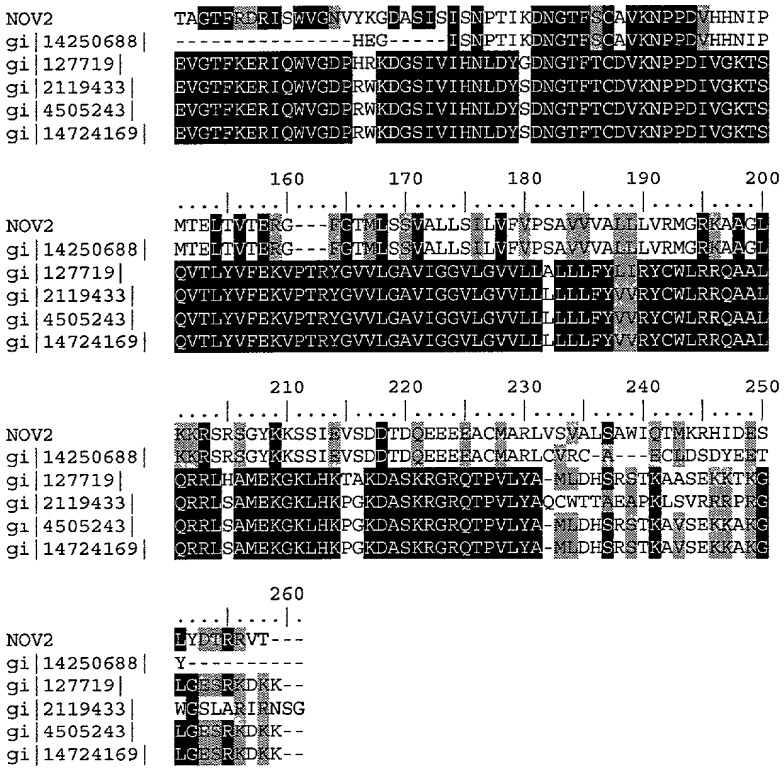
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|14250688 gb|AAH08810.1|AAH08810 (BC008810)	(protein for IMAGE:3948909) [Homo sapiens]	124	100	100	3e-54
gi|127719|sp|P10522|MYPO_BOVIN	(MYELIN PERIPHERAL PROTEIN) (MPP)	219	42	56	7e-21
gi|2119433|pir||I38053	myelin protein zero - human	251	35	52	4e-20
gi|4505243|ref|NP_000521.1| (NM_000530)	(Charcot-Marie-Tooth neuropathy 1B); Myelin protein zero [Homo sapiens]	258	35	52	5e-20
gi|14724169|ref|XP_042459.1| (XM_042459)	myelin protein zero [Homo sapiens]	248	35	52	5e-20

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 2D.

Table 2D. ClustalW Analysis of NOV2

1) NOV2 (SEQ ID NO:8)
2) Gi|14250688 (SEQ ID NO: 50)
3) Gi|127719 (SEQ ID NO:51)
4) Gi|2119433 (SEQ ID NO: 52)
5) Gi|4505243 (SEQ ID NO: 53)
6) Gi|14724169 (SEQ ID NO: 54)





Tables 2E-F list the domain description from DOMAIN analysis results against NOV2. This indicates that the NOV2 sequence has properties similar to those of other proteins known to contain this domain.

Table 2E Domain Analysis of NOV2

gnl|Smart smart00406, IGv, Immunoglobulin V-Type

CD-Length = 80 residues, 98.8% aligned Score = 50.4 bits (119), Expect = 1e-07

Myelin is an important insulating protein which protects nerve cells. Mutation of mylein proteins can cause a variety of neurological disorders. Pelizaeus-Merzbacher disease (PMD) and spastic paraplegia type 2 (SPG2) are X-linked developmental defects of myelin formation affecting the central nervous system (CNS). They differ clinically in the onset and severity of the motor disability but both are allelic to the proteolipid protein gene (PLP), which encodes the principal protein components of CNS myelin, PLP and its spliced isoform, DM20. 52 PMD and 28 SPG families without large PLP duplications or deletions were investigated by genomic PCR amplification and sequencing of the PLP gene. 29 and 4 abnormalities were discovered respectively. Patients with PLP mutations presented a large range of disease

severity, with a continuum between severe forms of PMD, without motor development, to pure forms of SPG. Clinical severity was found to be correlated with the nature of the mutation, suggesting a distinct strategy for detection of PLP point mutations between severe PMD, mild PMD and SPG. Single amino-acid changes in highly conserved regions of the DM20 protein caused the most severe forms of PMD. Substitutions of less conserved amino acids, truncations, absence of the protein and PLP-specific mutations caused the milder forms of PMD and SPG. Therefore, the interactions and stability of the mutated proteins has a major effect on the severity of PLP-related diseases. (See Cailoux et al., Eur J Hum Genet 2000 Nov;8(11):837-845).

A novel hereditary motor and sensory neuropathy (HMSN) phenotype, with partial steroid responsiveness, caused by a novel dominant mutation in the myelin protein zero (MPZ) gene has been discovered. Most MPZ mutations lead to the HMSN type I phenotype, with recent reports of Dejerine-Sottas, congenital hypomyelination, and HMSN II also ascribed to MPZ mutations. Differing phenotypes may reflect the effect of particular mutations on MPZ structure and adhesivity. Clinical, neurophysiological, neuropathological, and molecular genetic analyses of a family presenting with an unusual hereditary neuropathy were used. It was discovered that progressive disabling weakness, with positive sensory phenomena and areflexia, occurred in the proband with raised CSF protein and initial steroid responsiveness. Nerve biopsy in a less severely affected sibling disclosed a demyelinating process with disruption of compacted myelin. The younger generation were so far less severely affected, becoming symptomatic only after 30 years. All affected family members were heterozygous for a novel MPZ mutation (Ile99Thr), in a conserved residue. This broadens the range of familial neuropathy associated with MPZ mutations to include steroid responsive neuropathy, initially diagnosed as chronic inflammatory demyelinating polyneuropathy. (See Donaghy et al., J Neurol Neurosurg Psychiatry 2000 Dec;69(6):799-805)

The disclosed NOV2 nucleic acid of the invention encoding a myelin-like protein includes the nucleic acid whose sequence is provided in Table 2A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 2A while still encoding a protein that maintains its Myelin-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications

include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 39% percent of the bases may be so changed.

The disclosed NOV2 protein of the invention includes the Myelin-like protein whose sequence is provided in Table 2B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 2B while still encoding a protein that maintains its Myelin-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 64% percent of the residues may be so changed.

The NOV2 nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in neurological disorders, short stature, cancers, especially prostate cancer, metabolic disorders, inflammation and/or other pathologies and disorders. The NOV2 nucleic acid encoding myelin-like protein, and the myelin-like protein of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV2 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV2 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV2 epitope is from about amino acids 5 to 35. In another embodiment, a NOV2 epitope is from about amino acids 145 to 180. In additional embodiments, NOV2 epitopes are from about amino acids 220 to 240. These novel proteins can be used in assay systems for functional analysis of various human disorders, which are useful in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV3

A disclosed NOV3 nucleic acid of 5123 nucleotides (also referred to as CG122561227) encoding a novel vonWillebrand Factor (VWF)-like and kielin-like protein is shown in Table

3a. An open reading frame was identified beginning with a ATG initiation codon at nucleotides 4951-4948 and ending with a TGA codon at nucleotides 436-434.

Table 3A. NOV3 Nucleotide Sequence (SEQ ID NO:7)

GCTTTTTACCATACCAGGGAGCCCACCTCAACATGACTGTGGAAGACCAAAGGATATACCTAGGTTCAGA
TTATAATAAATCACCCAGCACCACCTGAATGTATTATCCACAAAGATATAGCAATAATAAAGGTTATATA
TACATATATTTATCTTGGTAACCTGAGGGCTAAAAACGTGGAATACGATAATTCTTCTCAAGAGGTCCAT
AGGGCCGGCGGCCGCAGGTCACGAAGCCTCCAAGACAGGTACACAGGTTGCAGGGTTCTCGGGGGTCTGG
GAACTCCTGGTTACTCAGGTAGGACTCCCCCAGGTACTCACAGCCATCACAGTCAGGGCAGCAGTCGCCC
CTGGCAGGGAAGGGGCACAGTGCAGGGGCACATGCCTTGGGCTCGCAGCTCACGCTGCCCTCCCAGCAAA
GGCAGAGGTGGCAGGCAGCAGTGGGCGATGGGAAGCGCTCCCCGCTGGCAAACTCCTTCCCCTGGTACAG
GCAGCCGTCGCAGGAGGGGCAGCAAGGCCCCTGGCGCGGGTGCGCGCAGGGCGCGGGCGGGCAGGGCAGC
CGCTGGCAGGACACGGAGCCGTCGAGGCAGAGGCAGCGGCGGCATGGATCGCCGGGCGGGGAGAAGTACT
CCTGGTGGCGGGCGTGGGCCGCGCCGGGCCGTGGGCAGCCGGCGGGGGCTGGGGCGGCTGCGGCGAGACA
GCGCATCAAAGGGGCCCAGGAACAGGCCTCCGAGGGGACCCCCAGGGAGGAGCAGCCGAGGGGTGCGGCC
CCTACCTGGGCACTGCGGGCAGCACTCTCCCGGCAGCAGGACAGGCTCAGACAGCGACACAGACGGCAGG
GGTCAGAGGGGTGGGGGAAGTCCGCTCCGCTGGGGTACTCTTTCCCGCCAAAGGCACAGCCGCTGCAGTC
GTTCGGGCAGCAGGTCCCAGGCAGCGGGTGGGCACAGGGGGCCCTGGGGCAGGGGCGAGGCTGGCAGTGG
GCATGGCCTTCCTGGCATCGGCACTCCTGGCAGGGGTCTCGGGGGTGGGAGAAGCTCTCGCCGTCCACAA
ACACCTCTTCCTCCAGGATGCAGTCTGGGGGGTAGGGGGGTGGGGGCCCTAGCGTGGTGGGGCGGGGGGC
AGTAGTTACTGGGCACCTGGGGCAACACTGGCCTGGTCCACTCTGGGGCCTGGCACAGGTCGTGGGAGGG
CAGTCAACCAAGGAGCATGTCACAGTTCCATCCTGACAGTGGCAGGCATGGCAAGGGCTGTCTGCATCCG
TGAAGTTCTGCCCATTGGCATACACTTGGCTGTGGTAGGTGCAGCTGTCACAGCTGGGGCAGCAGGCACC
AGGGGGCTGGGTGGGGTGCTGGCAGGGGGCTGGGGGGCAGAGCACAGCCCCGCACTTGGGTACCCCATCT
TGACAGACGCAGGCGGTGCAGGGCCGACCATCAGGCTCCCACTGGACTCCCTCAGCAAACTCCTCTCCAT
CCAGCTCACAGGCTGGGCAGAGCTGGCGGCCAGAGGCAGGCAGGGCACAGGGGGTGACTGGGCACTCCTG
CTCCTCACAGGAGACCTCGCCAGCCTGGCAGGAGCAGCGGACACAGAGGCCCCGCTCTTGGAGTCTGAAG
GTCTCCTGGCTCTGATACTGGTGTCCCTGGTACTCACAGCCTGGATGTGACCCTCCCGGAGCCGCTGCTG
CTCGCGGTCCCGCCGCGGCGCTGCCGCCTGCCGCGCTGTGCAGCTCCAGCAGCCGCTGCAGAGCCGTCAC
CTGCTGCGCCGCGCTTAAGCCCGCAGGCGCCTTGGCGGTGCTGAGGGGCGCCGGCCACGCGGCCTTCAAG
GCCTCCTGCTCCCCCGGTGCGGGGCCCACTCCAGGGCCCTGCAGCCCGTGCGGATCGCGCTCCAGGCCTG
GGGGCCCCGGAGAGCCCCGAGGAGCCCCTGCTGCCCGGATACCTCGGCGCGCAGGGTCGCTGGCATCTCG
GCTCCGGCTCCGCGACCTGGGAGCCGCCGCCGGGCCGGGGGCTTCGGGCGGGTAAGCGCAGCCCACGCCC
CCTCCCGGGCGGCCCCCAGCTTTGCCACCGCCGGTGCCGACCTTTGTGGCTCGCCTTTGATCATGCTCTG
CGTCAGCGTGGTAGTCCTTCTCCGGAGGTTTGGGCTCTCCCTGCCCACAGGCTTTGGAGTCTGTGCTTTC
AGGGACCCGCAGGAGTCCCTCGGATGGGCTGAGGGGTCTCCGCTTTCTGATCCTGAGGGTCCTCCTCTCA
GACTCAGGGGTGTCCATCCTTGGTGGTCTTTGAAGTTCTGCTCTCTCCTGGCCCAGGTGCGGGTCCGAGC
CCAGCCCTTCAAGGGCATCTTGGGAAGGCAGGTTTTGGGAGGGCAGGTCCCCCGGCCCAGGGGTCCCGGG
AGTGAGCTTTCTTTTCTGGGTCTCAGGCTCTGCCTCACTCCTCTCTTCCCTCTGGGCCAGGTCCGGCTGC
TCAGGGTCCCCACCTGTGCTACCACCTGGCTGACAGCACTGGCTCCATGCTTGCTGGGCCTGGCCCCTCG
GACCGAAAAACTGGGCCTGGGGTGGCCAGAAGAGGCCCAGCTCCACACCAGTCAGCAGTTCCAAGTCCCA
CAGGAGCTGCTCCTGGGCCCGCCGGCTCCACTCCATCTGCAGCAGTACAGGGGGCAGCTCCAGCCCTGGG
GGATACCCGCGGCCCTCTTGCACGCAGTGGGCTGCCAGCTCCCCCAGGGGGATATGCTGATTGAAGCAGG
TGCGGGGACAGGGTGGGCCGCACTCATCAAACACGAAGCCACGCTCCAGGGGGCAGCCTACCACACACAG
CGTGGGGCCTCGCCAGGTAGGTGTCACTCCTGCCTGGCGACAGTGACTGGCGTAGGCTTCCAGGGCATCA
CAGAGGCAGGCATCAGCGGAGGAGCCAGGGCCACAGGCACACAGGTCATACACACAGGCGGCAAAGAAGG
GCTCCGGTGGCACCACAGCATGGCAGCGACTGAATGGGGAGGACTTCAGCACCCCACACCGGGCATTGGC
CTCACGCCTGGCACGGTAACCTGCTGCCCGGCACGGATCCACCTCTCGGCCTGCAGAACAGGGCCGGCCA
GGCCACAGCCCCTCTGAGACCTGCCAGCTATTCCCAAACGCAGCCTCCGAGGGCAGGAGCAGCCCCTCAG
GGCCCTGCAGATCGTCCTGGGCAAAGCCATTGAAGTTCCCACAGAGCCCACAAGTCCGGCCCTGGTAGGA
GCCAGGTACGCTCACCTCCACCTGGGACTGCCCATCCCACAGCACCTGGAGCCCGGGCTGGGCGTGCAGG
ATCACAGTGTGTCCTCGCAGCTCCACATACAGCAGCGGCTCCTGCAGGAAGGGCAAGGCCACCGGGTGCC
CATCCACCGTGACTGCCCCGTCCTGCAGCAGCCGCACGGCCATGTCTCCCAGCAGCACCGCCACCTCCTG
GGTCCAGGCCACACTGCTCCGGCCCCGGTCATCATTGGTCACGTGCACACTGAAGTCCCCGCTGTGGCAG
TCCTTGGCCAGCACATAGCTGCAACTGCTCTGGAAGTGCAGCAGGCGGCCGTCGAAGGTGCGGTAATGGG
GGTCTCCGAAGGCCATGCAGGAAGCGGGCCGAGGCAGGCAGCGGGGGCAGCAGCTGCCAGGACTCAGGGC
AGGGGCCTTGTCGGGGCCACACGAGAGCGGTGAGCAGCGCTGGCTCTGGCAACGCACGGTGCCCGCCATG
CAGGAGCAGCTGGTGCAGGTGTCCACAGTCCAGCGCTCTCCAGAGGCCACCTCACGGCCCTGGTGCACGC
AGGACTGGGTGGGAGCTTGGCATCGCTCACAGCAGCTGTCAGCCTGGGGCACCTTCGCCCAGCCATGGGG
GCAGGAGAGGGCCTGGCACTCCTCGAGGTGGCACTCCACATGGCCCCGATGGCAGGTGCAGGCGATGCAC
GCATTGCTGGGGTCCCGCCAGCTCTCTCCATCTGCCACTCTCCGGCCCTCGGCCTCCACCACACATTCCC
GGCATACGGGGCAGCAGCTCCCAGGGGGAGTGTGGCGCTCTGAGAGGGGACAGCTGAGCTCAGGACAAGC
CTGGTGGATGCAGAGCCATGTCAGGTCCTGGCACTGGCACGTGTAGCAGGGGTCTGGTGGGGCTAGCTCA
GATCCCAGCAGGCCCTCTGAACAGTTACTCAAGGCCTCGGCACAGGTGGGACAGCAGTGCTGGGGCCCAG
GGGGCAGGAGCTGGCTGGGGGGGCAGCCCACCAGGCTGGGACACTGCCGCCGGTGACAGCGAAGGCTGGG

AGGCCCCTCAGGCTGTGGCTCGCAGATGCACACTTCACAGGGGTCTGCCCCAGGCTGGAAGCTCTCCCCA
GGCTCGTACTTCCGGCCCTCATGCTCACAGTCAGAGCATTGAGGACAGCAGTCATGGGGCCCTTGGCGGG
GCTGGGCGCAAGAGCTGATGCACTGGATGCGTGCACAGGTGACGACGCCCTCGTGACACACACAGGAGGA
GCAGGCACTGTCGGGGGGCACCCATCTACTGCCTTCGGGGTGCTCTTCCCCATGAGCCAGGCAGCCTGCT
CTCAAGACCAAGCTCCAGGCAGCAGGCACTGCCCAGTGCAGCCCGCACCGGCCACAGACCTGGCATGCAG
CAGCTGTGTCATAAATGCATGTGGACCAGGTGAATGGCTCCATCGCTAACCATGTGCCCAAGGTAACTCA
GTCTCTCCGGGCCTCAGTCTCCTCATCTGTTAAATGGGGATTTCCTCTGTCCTGCCTCCCTCCCAGAGCA
AGTGAAATGCTATGACAGTTCTGTGGTTCTGTAGAAACACCACCACACTGCGCAGGGTGTGGGACGAGGG
GGCAGTGGGCAGGCTAAGAAAGGCTCAAGTTCAGAGCCAGATGGTCCAAGTGTCCATCTTGACTCTGCCA
CCTTCTCTACCTCTCTGTACCTCCACTTTCTCGTCTGTAAAATAGGAGGACTAAGAGTGCTTATCTGGTA
AGTTGTTGTGCTGATTAAATGAGATAATACACGTAAAGTGCTCAGGGCCTGGCACATGCTACCTGCTCAC
TGAATGTCAGGTATCTTGATGATGATGATGATGGTGGTGATGATGATGATGATGATGAATGGGGTGTGGT
TAGGAAGAGGGGC

The disclosed NOV3 nucleic acid sequence maps to chromosome 7 and has 1074 of 1729 bases (62%) identical to a gb:GENBANK-ID:AB026192|acc:AB026192.1 mRNA from Xenopus laevis (Xenopus laevis mRNA for Kielin, complete cds).

A disclosed NOV3 protein (SEQ ID NO:10) encoded by SEQ ID NO:9 has 1497 amino acid residues, and is presented using the one-letter code in Table 3B. Signal P, Psort and/or Hydropathy results predict that NOV3 does have a signal peptide, and is likely to be localized to the nucleus with a certainty of 0.6000. In other embodiments NOV3 is also likely to be localized to the mitochondrial matrix space with a certainty of 0.4270, to the mitochondrial inner membrane with a certainty of 0.1047, or to the mitochondrial inner membrane space with a certainty of 0.1047. The most likely cleavage site for NOV3 is between positions 43 and 44, (CLA-HG).

Table 3B. Encoded NOV3 protein sequence (SEQ ID NO:8).

MEPFTWSTCIYDTAAACQVCGRCGLHWAVPAAWSLVLRAGCLAHGEEHPEGSRWVPPDSACSSCVCHEGV
VTCARIQCISSCAQPRQGPHDCCPQCSDCEHEGRKYEPGESFQPGADPCEVCICEPQPEGPPSLRCHRRQ
CPSLVGCPPSQLLPPGPQHCCPTCAEALSNCSEGLLGSELAPPDPCYTCQCQDLTWLCIHQACPELSCPL
SERHTPPGSCCPVCRECVVEAEGRRVADGESWRDPSNACIACTCHRGHVECHLEECQALSCPHGWAKVPQ
ADSCCERCQAPTQSCVHQGREVASGERWTVDTCTSCSCMAGTVRCQSQRCSPLSCGPDKAPALSPGSCCP
RCLPRPASCMAFGDPHYRTFDGRLLHFQSSCSYVLAKDCHSGDFSVHVTNDDRGRSSVAWTQEVAVLLGD
MAVRLLQDGAVTVDGHPVALPFLQEPLLYVELRGHTVILHAQPGLQVLWDGQSQVEVSVPGSYQGRTCGL
CGNFNGFAQDDLQGPEGLLLPSEAAFGNSWQVSEGLWPGRPCSAGREVDPCRAAGYRARREANARCGVLK
SSPFSRCHAVVPPEPFFAACVYDLCACGPGSSADACLCDALEAYASHCRQAGVTPTWRGPTLCVVGCPLE
RGFVFDECGPPCPRTCFNQHIPLGELAAHCVQEGRGYPPGLELPPVLLQMEWSRRAQEQLLWDLELLTGV
ELGLFWPPQAQFFGPRGQAQQAWSQCCQPGGSTGGDPEQPDLAQREERSEAEPETQKRKLTPGTPGPGDL
PSQNLPSQDALEGLGSDPHLGQERAELQRPPRMDTPESERRTLRIRKRRPLSPSEGLLRVPESTDSKACG
QGEPKPPEKDYHADAEHDQRRATKVGTGGGKAGGRPGGGVGCAYPPEAPGPAAAPRSRSRSRDASDPARR
GIRAAGAPRGSPGPPGLERDPHGLQGPGVGPAPGEQEALKAAWPAPLSTAKAPAGLSAAQQVTALQRLLE
LHSAAGGSAAAGPRAAAAPGGSHPGCEYQGHQYQSQETFRLQERGLCVRCSCQAGEVSCEEQECPVTPCA
LPASGRQLCPACELDGEEFAEGVQWEPDGRPCTACVCQDGVPKCGAVLCPPAPCQHPTQPPGACCPSCDS
CTYHSQVYANGQNFTDADSPCHACHCQDGTVTCSLVDCPPTTCARPQSGPGQCCPRCPVTTAPRPTTLGP
PPPYPPDCILEEEVFVDGESFSHPRDPCQECRCQEGHAHCQPRPCPRAPCAHPLPGTCCPNDCSGCAFGG
KEYPSGADFPHPSDPCRLCRCLSLSCCRESAARSAQVGAAPLGCSSLGVPSEACSWAPLMRCLAAAAPAP
AGCPRPGAAHARHQEYFSPPGDPCRRCLCLDGSVSCQRLPCPPAPCAHPRQGPCCPSCDGCLYQGKEFAS
GERFPSPTAACHLCLCWEGSVSCEPKACAPALCPFPARGDCCPDCDGCEYLGESYLSNQEFPDPREPCNL
CTCLGGFVTCGRRPYGPLEKNYRIPRF

The disclosed NOV3 amino acid has 359 of 642 amino acid residues (55%) identical to, and 457 of 642 amino acid residues (71%) similar to, the 2327 amino acid residue ptnr:SPTREMBL-ACC:Q9IBG7 protein from Xenopus laevis (African clawed frog) (KIELIN).

The NOV3 sequence is predicted to be expressed in the Adrenal Gland/Suprarenal gland, Amygdala, Aorta, Bone, Bone Marrow, Brain, Cerebellum, Cervix, Chorionic Villus,Cochlea, Colon, Dermis, Epidermis, Foreskin, Hair Follicles, Heart, Hippocampus, Hypothalamus, Kidney, Liver, Lung,Lymph node, Lymphoid tissue, Mammary gland/Breast, Muscle, Myometrium, Ovary, Pancreas, Parotid Salivary glands,Pituitary Gland, Placenta, Prostate, Proximal Convoluted Tubule, Small Intestine, Spinal Chord, Spleen, Stomach,Substantia Nigra, Testis, Thymus, Thyroid, Tonsils, Umbilical Vein, Urinary Bladder, Uterus.

NOV3 also has homology to the amino acid sequences shown in the BLASTP data listed in Table 3C.

Table 3C. BLAST results for NOV3

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|7768636|dbj|BAA95483.1 (AB026192)	Kielin [Xenopus laevis]	2327	55	70	e-177
gi|9864185|gb AAG01337.1|AF288223 1 (AF288223)	Crossveinless 2 [Drosophila melanogaster]	751	32	44	4e-69
gi|7291288|gb AAF46719.1| (AE003453)	CG15671 gene product [Drosophila melanogaster]	555	32	45	3e-55
gi|12851935|db|BAB29213.1| (AK014221)	Putative protein/mouse	452	34	48	1e-51
gi|12667418|gb|AAK01435.1 AF332979 1 (AF332979)	Sonadhesion variant 5/human	2501	34	47	2e-39

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 3D.

Table 3D. ClustalW Analysis of NOV3

1) NOV3 (SEQ ID NO:10)
2) gi|7768636| (SEQ ID NO: 55)
3) gi|9864185| (SEQ ID NO: 56)
4) gi|7291288| (SEQ ID NO: 57)

5) gi|12851935| (SEQ ID NO: 58)
6) gi|12667418| (SEQ ID NO: 59)

```
                        10        20        30        40        50
                ....|....|....|....|....|....|....|....|....|....|
NOV3            --------MEPFTWSTCIYDTAAACQVCGR--------------------
gi|7768636|     MNTLLWTILLPLLFSFCVCQQPEHQDLEMS--------------------
gi|9864185|     ----------------------------------------------------
gi|7291288|     ----------------------------------------------------
gi|12851935|    ----------------------------------------------------
gi|12667418|    MVPPVWTLLLLVGAALFRKEKPPDQKLVVRSSRDNYVLTQCDFEDDAKPL

                        60        70        80        90       100
                ....|....|....|....|....|....|....|....|....|....|
NOV3            CGLHWAVPAAWSLVLRAGCLAHGEEHPEGSRWVPPDSACSSCVCHEGVVT
gi|7768636|     VQYYDDNVIDLLEALNVTRSVKGVTKAKGSDPASPAWKFRQRVPHLTLPR
gi|9864185|     ----------------------------------------------------
gi|7291288|     ----------------------------------------------------
gi|12851935|    ----------------------------------------------------
gi|12667418|    CDWSQVSADDEDWVRASGPSPTGSTGAPGGYPNGEGSYLHMESNSFHRGG

                       110       120       130       140       150
                ....|....|....|....|....|....|....|....|....|....|
NOV3            CARIQCISSCAQPRQGPHDCCPQCSDCEHEGRKYEPGESFQPGADPCEVC
gi|7768636|     DYSVYLLSTTQES-LGLHFVAKQAKNNRGTLVAFLSPAATKIDGRPLLRL
gi|9864185|     ----------------------------------------------------
gi|7291288|     ----------------------------------------------------
gi|12851935|    ----------------------------------------------------
gi|12667418|    VARLLSPDLWEQGPLCVHFAHHMFGLSWGAQLRLLLLSGEEGRRPDVLWK

                       160       170       180       190       200
                ....|....|....|....|....|....|....|....|....|....|
NOV3            ICEPQP-E------GPPSLRCHRRQCPSLVGCPPSQLLPPGPQHCCPTCA
gi|7768636|     ISDTHTDQLYFEYRTAQTMEPASLHFPGSSPFSGSQWARVALNVNTHKVT
gi|9864185|     ----------------------------------------------------
gi|7291288|     ----------------------------------------------------
gi|12851935|    ----------------------------------------------------
gi|12667418|    HWNTQRPS----WMLTTVTVPAGFTLPTRLMFEGTRGSTAYLDIALDALS

                       210       220       230       240       250
                ....|....|....|....|....|....|....|....|....|....|
NOV3            EALSNCSEGLLGSELAPPDP------------------------------
gi|7768636|     LFLDCEEPVVFGKEGAEEMLSLILPLDLEITFA--------STPSDKESK
gi|9864185|     ----------------------------------------------------
gi|7291288|     ----------------------------------------------------
gi|12851935|    ----------------------------------------------------
gi|12667418|    IRRGSCNRVCMMQTCSFDIPNDLCDWTWIPTASGAKWTQKKGSSGKPGVG

                       260       270       280       290       300
                ....|....|....|....|....|....|....|....|....|....|
NOV3            ----CYTCQCQDLTWLCIHQACPELSCPLSERHTPPGSCCPVCRECVVEA
gi|7768636|     FLGYWQTAEISPTGFTRRPWHCENRSDSLPLPYSLSGERQMEDEEIQREP
gi|9864185|     ----------------------------------------------------
gi|7291288|     ----------------------------------------------------
gi|12851935|    ----------------------------------------------------
gi|12667418|    PDGDFSSPGSGCYMLLDPKNARPGQKAVLLSPVSLSSGCLSFSFHYILRG

                       310       320       330       340       350
                ....|....|....|....|....|....|....|....|....|....|
NOV3            EGRRVADGESWRDPSNACIACTCHRGHVECHLEECQALSCPHG------W
gi|7768636|     RAPDLSDTDHYQQQQSEVPAQLLAKDDRLQRLEEAVKGLTNMIDMIKSQN
gi|9864185|     ----------------------------------------------------
gi|7291288|     ----------------------------------------------------
gi|12851935|    ----------------------------------------------------
gi|12667418|    QSPG-AALHIYASVLGSIRKHTLFSGQPGPNWQAVSVNYTAVGRIQFAVV

                       360       370       380       390       400
                ....|....|....|....|....|....|....|....|....|....|
NOV3            AKVPQADSCCERCQAPTQSCVHQGREVASGERWTVDTCTSCSCMAGTVRC
gi|7768636|     ADLQARVIALESCECRRSTCVWEDKEYQDSETWKKDACNICVCVGGSVTC
gi|9864185|     ----------------------------------------------------
gi|7291288|     ----------------------------------------------------
gi|12851935|    ----------------------------------------------------
gi|12667418|    GVFGKTPEPAVAVDATSIAPCGEGFPQCDFEDNAHPFCDWVQTSGDGGHW

                       410       420       430       440       450
                ....|....|....|....|....|....|.. .|....|....|....|
NOV3            QSQRCSPLSCG-----------PDKAPALSPGSCCPRCLPRPASCMAFG
```

```
gi|7768636|   SVRKDWPQCLGC------FHEGRNYNNKDIFSVGPCMSCICQSGEVSCTP
gi|9864185|   --------------------------------------------------
gi|7291288|   --------------------------------------------------
gi|12851935|  --------------------------------------------------
gi|12667418|  ALGHKNGPVHGMGPAGGFPNAGGHYIYLEADEFSQAGQSVRLVSRPFCAP

                       460       470       480       490       500
                ....|....|....|....|....|....|....|....|....|....|
NOV3            DPHYRTFDGRLLHFQSSCSYVLAKDCHSG--------DFSVHVTNDDRGR
gi|7768636|   KLCPPVTCSDPVTLPNECCPLCATGCSDGHKEGDTWRKDTCTTCTCQNGT
gi|9864185|   --------------------------------------------------
gi|7291288|   --------------------------------------------------
gi|12851935|  --------------------------------------------------
gi|12667418|  GDICVEFAYHMYGLGEGTMLELLLGSPAGSPPIPLWKRVGSQRPYWQNTS

                       510       520       530       540       550
                ....|....|....|....|....|....|....|....|....|....|
NOV3            SSVAWTQEVAVLLGDMAVRLLQDGAVTVDGHPVALPFLQEPLLYVELRGH
gi|7768636|   ISCEREQCPELTCLKRHTPPGQCCAKCQQGCEYEGLIYRNGDYFLSQSNP
gi|9864185|   --------------------------------------------------
gi|7291288|   --------------------------------------------------
gi|12851935|  --------------------------------------------------
gi|12667418|  VTVPSGHQQPMQLIFKGIQGSNTASVVAMGFILINPGTCPVKVLPELPPV

                       560       570       580       590       600
                ....|....|....|....|....|....|....|....|....|....|
NOV3            TVILHAQPGLQVLWDGQSQVEVSVPGSYQGRTCGLCGNFNGFAQDDLQGP
gi|7768636|   CVNCSCLNNLVRCLPVQCPLPACTNPVPIPGQCCPSCPVCELDGHPLIPG
gi|9864185|   --------------------------------------------------
gi|7291288|   --------------------------------------------------
gi|12851935|  --------------------------------------------------
gi|12667418|  SPVSSTGPSETTGLTENPTISTKKPTVSIEKPSVTTEKPTVPKEKPTIPT

                       610       620       630       640       650
                ....|....|....|....|....|....|....|....|....|....|
NOV3            EGLLLPSEAAFG----NSWQVSEGLWPGRPCSAGREVDPCRAAGYRARRE
gi|7768636|   QNVTTKDGCRLCSCQDGKVQCTESVQCPHICTHGVRSNSCCLDCSACEMH
gi|9864185|   --------------------------------------------------
gi|7291288|   --------------------------------------------------
gi|12851935|  --------------------------------------------------
gi|12667418|  EKPTISTEKPTIPSEKPNMPSEKPTIPSEKPTILTEKPTIPSEKPTIPSE

                       660       670       680       690       700
                ....|....|....|....|....|....|....|....|....|....|
NOV3            ANARCG---VLKSS--PFSRCHAVVPPEPFFAACVYDLCACGPGSSADAC
gi|7768636|   GDIIPNGL-TFQGNMDPCESCTCQDGNVHCVRVSCPELSCVLHEKIPGEC
gi|9864185|   --------------------------------------------------
gi|7291288|   --------------------------------------------------
gi|12851935|  --------------------------------------------------
gi|12667418|  KPTISTEKPTVPTEEPTTPTEETTTSMEEPVIPTEKPSIPTEKPSIPTEK

                       710       720       730       740       750
                ....|....|....|....|....|....|....|....|....|....|
NOV3            LCDALEAYASHCRQAGVTPTWRGPTLCVVGCPLER--GFVFDECGPPCPR
gi|7768636|   CSQCQSCMDGTVKRKHGEEWKPQGDPCQSCRCLEGRVQCRKRHCAALCRN
gi|9864185|   --------------------------------------------------
gi|7291288|   --------------------------------------------------
gi|12851935|  --------------------------------------------------
gi|12667418|  PTISMEETIISTEKPTISPEKPTIPTEKPTIPTEKSTISPEKPTTPTEKP

                       760       770       780       790       800
                ....|....|....|....|....|....|....|....|....|....|
NOV3            TCFNQHIPLGELAAHCVQEGRGYPPG-----LELPPVLLQMEWSRRAQEQ
gi|7768636|   PLPPRPGTCCPMCDGCLYNGRSY--------LNGQPVRSTDQCNRCFCEN
gi|9864185|   --------------------------------------------------
gi|7291288|   --------------------------------------------------
gi|12851935|  --------------------------------------------------
gi|12667418|  TIPTEKPTISPEKPTTPTEKPTISPEKLTIPTEKPTIPTEKPTIPTEKPT

                       810       820       830       840       850
                ....|....|....|....|....|....|....|....|....|....|
NOV3            LLWDLELLTGVELGLFWPPQAQFFGPRGQAQQAWSQCCQPGGSTGGDPEQ
gi|7768636|   GNVQCEPIACPQAPCRNPVRRTGECCPRCEGCEYDSRHFAEGVVFTTAHD
gi|9864185|   --------------------------------------------------
gi|7291288|   --------------------------------------------------
gi|12851935|  --------------------------------------------------
gi|12667418|  ISTEEPTTPTEETTISTEKPSIPMEKPTLPTEETTTSVEETTISTEKLTI
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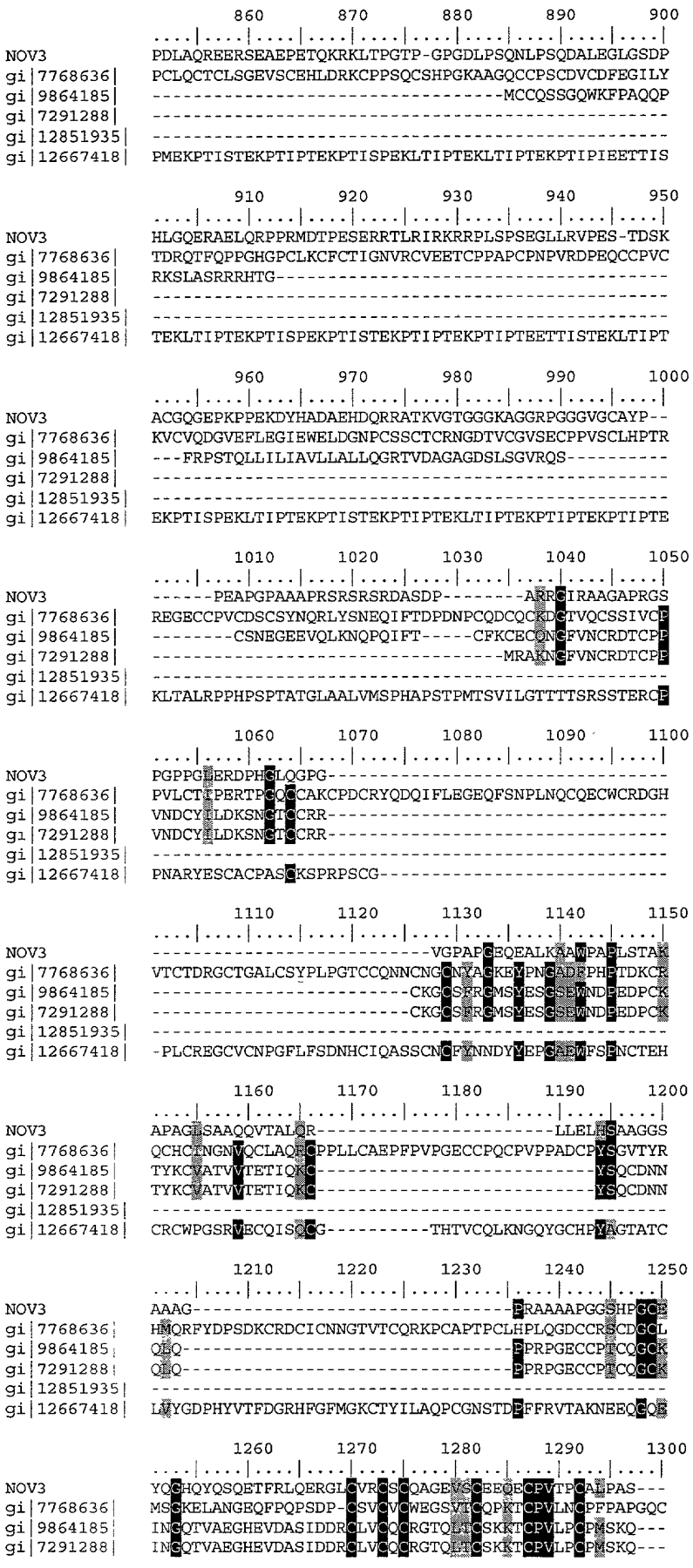

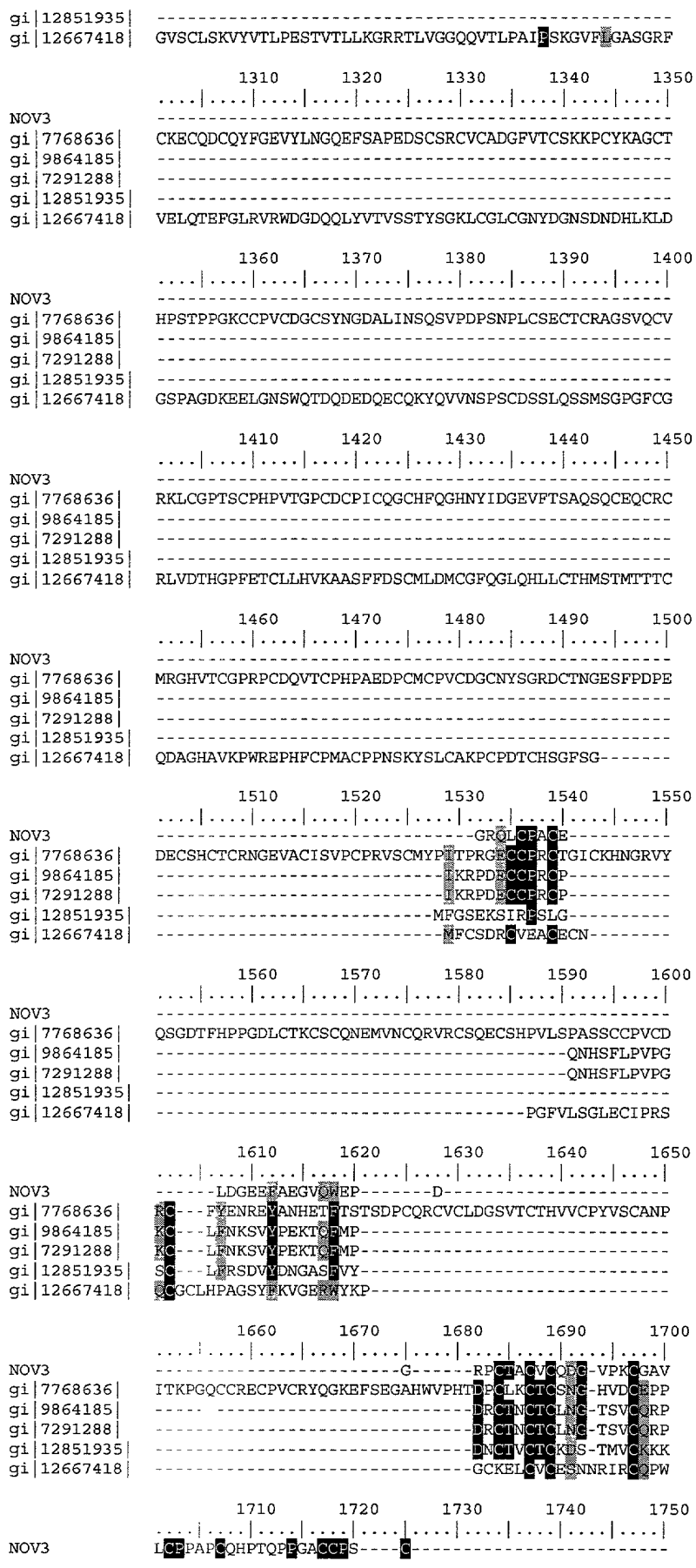

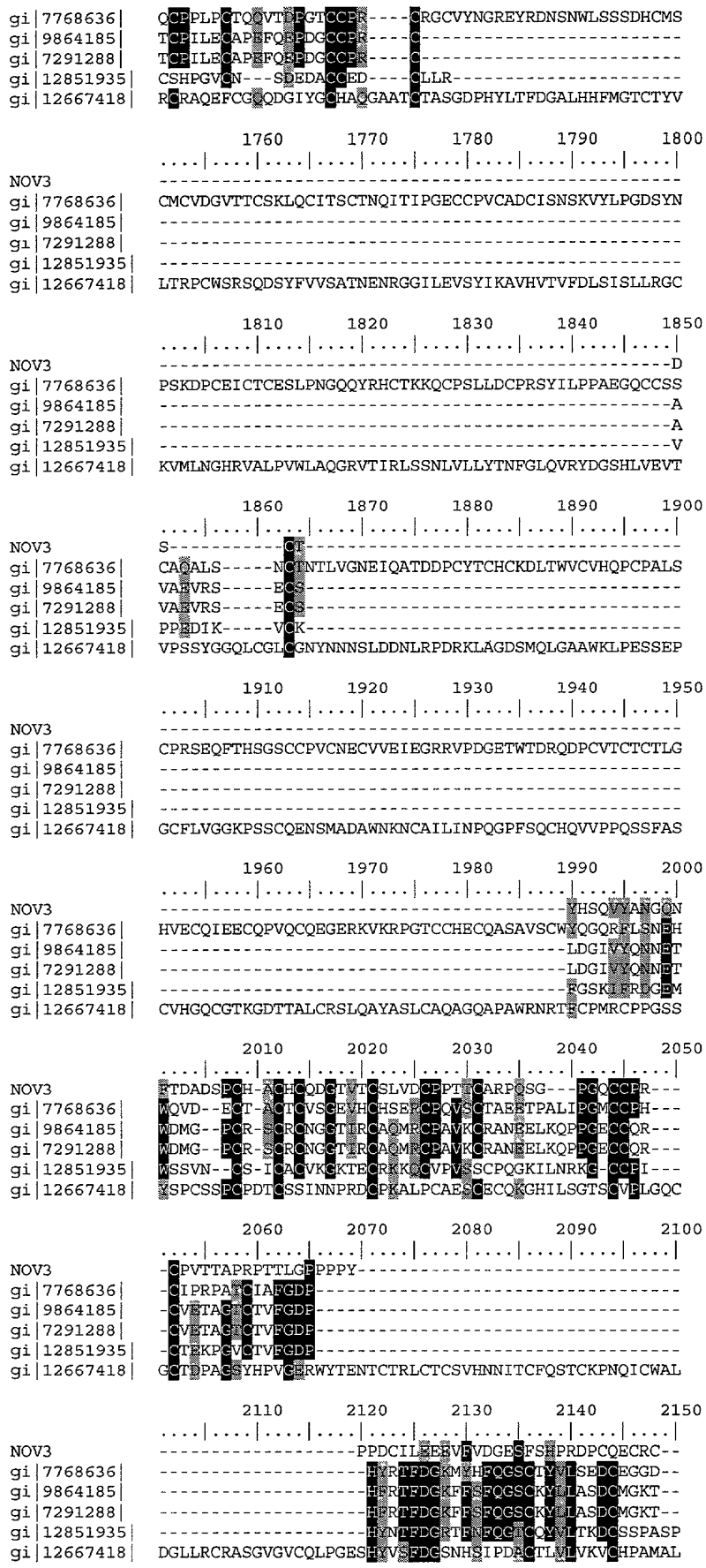

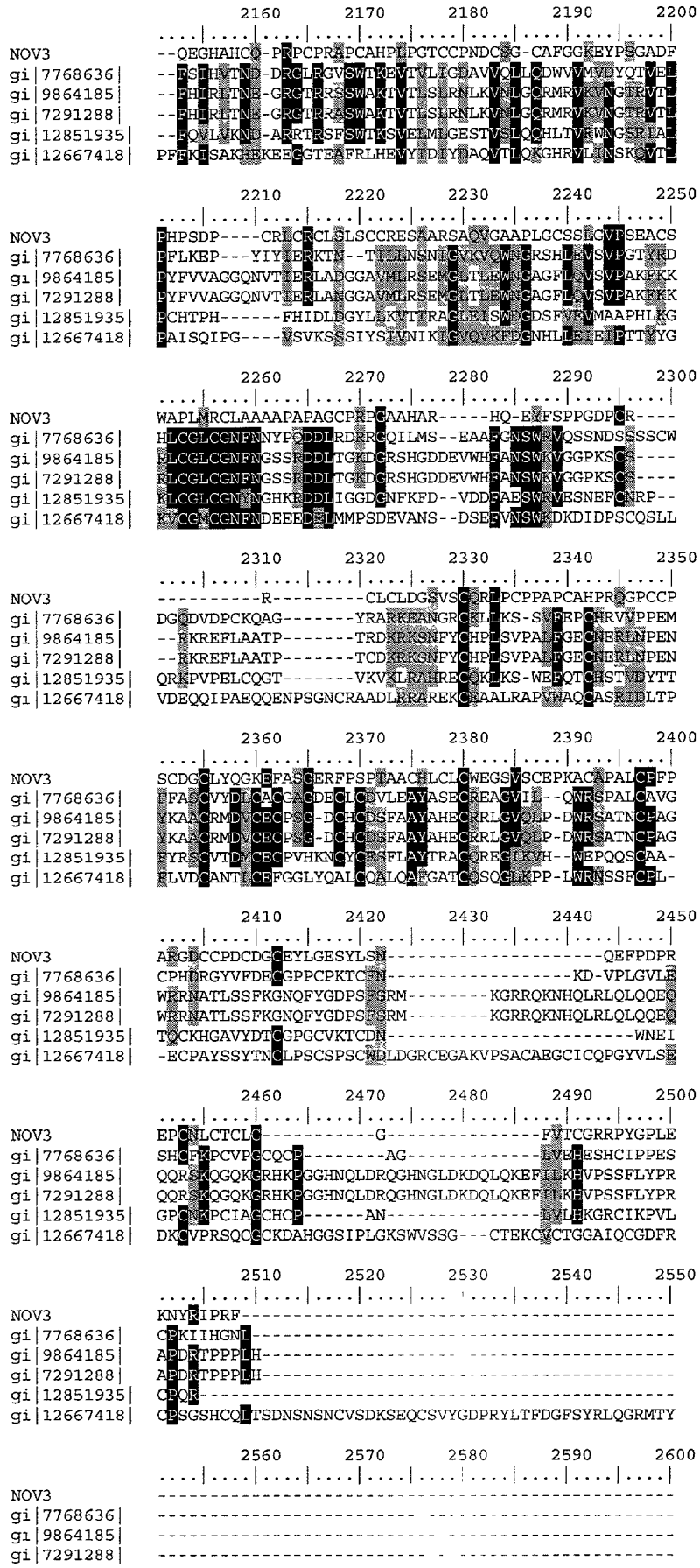
2160 2170 2180 2190 2200
NOV3
gi|7768636|
gi|9864185|
gi|7291288|
gi|12851935|
gi|12667418|
2210 2220 2230 2240 2250
NOV3
gi|7768636|
gi|9864185|
gi|7291288|
gi|12851935|
gi|12667418|
2260 2270 2280 2290 2300
NOV3
gi|7768636|
gi|9864185|
gi|7291288|
gi|12851935|
gi|12667418|
2310 2320 2330 2340 2350
NOV3
gi|7768636|
gi|9864185|
gi|7291288|
gi|12851935|
gi|12667418|
2360 2370 2380 2390 2400
NOV3
gi|7768636|
gi|9864185|
gi|7291288|
gi|12851935|
gi|12667418|
2410 2420 2430 2440 2450
NOV3
gi|7768636|
gi|9864185|
gi|7291288|
gi|12851935|
gi|12667418|
2460 2470 2480 2490 2500
NOV3
gi|7768636|
gi|9864185|
gi|7291288|
gi|12851935|
gi|12667418|
2510 2520 2530 2540 2550
NOV3
gi|7768636|
gi|9864185|
gi|7291288|
gi|12851935|
gi|12667418|
2560 2570 2580 2590 2600
NOV3
gi|7768636|
gi|9864185|
gi|7291288|

```
gi|12851935|  ------------------------------------------------
gi|12667418|  VLIKTVDVLPEGVEPLLVEGRNKMDPPRSSIFLQEVITTVYGYKVQLQAG

                      2610      2620      2630      2640      2650
              ....|....|....|....|....|....|....|....|....|....|
NOV3          ------------------------------------------------
gi|7768636|   ------------------------------------------------
gi|9864185|   ------------------------------------------------
gi|7291288|   ------------------------------------------------
gi|12851935|  ------------------------------------------------
gi|12667418|  LELVVNNQKMAVPYRPNEHLRVTLWGQRLYLVTDFELVVSFGGRKNAVIS

                      2660      2670      2680      2690      2700
              ....|....|....|....|....|....|....|....|....|....|
NOV3          ------------------------------------------------
gi|7768636|   ------------------------------------------------
gi|9864185|   ------------------------------------------------
gi|7291288|   ------------------------------------------------
gi|12851935|  ------------------------------------------------
gi|12667418|  LPSMYEGLVSGLCGNYDKNRKNDMMLPSGALTQNLNTFGNSWEVKTEDAL

                      2710      2720      2730      2740      2750
              ....|....|....|....|....|....|....|....|....|....|
NOV3          ------------------------------------------------
gi|7768636|   ------------------------------------------------
gi|9864185|   ------------------------------------------------
gi|7291288|   ------------------------------------------------
gi|12851935|  ------------------------------------------------
gi|12667418|  LRFPRAIPAEEEGQGAELGLRTGLQVSECSPEQLASNSTQACRVLADPQG

                      2760      2770      2780      2790
              ....|....|....|....|....|....|....|....|....|.
NOV3          ---------------------------------------------
gi|7768636|   ---------------------------------------------
gi|9864185|   ---------------------------------------------
gi|7291288|   ---------------------------------------------
gi|12851935|  ---------------------------------------------
gi|12667418|  PFAACHQTVAPEPFQEHCVLDLCSAQDPREQEELRCQVLSGWAAAF
```

Table 3E lists the domain description from DOMAIN analysis results against NOV3. This indicates that the NOV3 sequence has properties similar to those of other proteins known to contain this domain.

Table 3E Domain Analysis of NOV3

gnl|Smart|smart00216,
CD-Length = 162 residues, 99.4% aligned Score = 139 bits (351), Expect = 9e-34

Von Willebrand factor domains are present in a number of proteins important for growth and cell division. One such protein, Kielin, is important for early embryonic development, and may be an excellent target for cancer. The midline tissues are important inductive centers of early vertebrate embryos. By signal peptide selection screening, we isolated a secreted factor, Kielin, which contains multiple cys-rich repeats similar to those in chordin (Chd). Expression of Kielin starts at midgastrula stages in the notochord and is detected in the floor plate of neurula embryos. Kielin is induced in mesoderm and in ectoderm

by nodal-related genes. Chd is sufficient to activate Kielin expression in mesoderm whereas Shh or HNF-3beta in addition to Chd is required for induction in ectoderm. Kielin has a distinct biological activity from that of Chd. Injection of Kielin mRNA causes dorsalization of ventral marginal zone explants and expansion of MyoD expression in neurula embryos. Unlike Chd, Kielin does not efficiently induce neural differentiation of animal cap ectoderm, suggesting that the activity of Kielin is not simply caused by BMP4 blockade. Kielin is a signaling molecule that mediates inductive activities of the embryonic midline. (See Matsui et al., Proc Natl Acad Sci U S A 2000 May 9;97(10):5291-6).

The disclosed NOV3 nucleic acid of the invention encoding a VWF-like and kielin-like protein includes the nucleic acid whose sequence is provided in Table 3A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 3A while still encoding a protein that maintains its VWF-like and kielin-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 38 percent of the bases may be so changed.

The disclosed NOV3 protein of the invention includes the VWF-like and kielin-like protein whose sequence is provided in Table 3B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 3B while still encoding a protein that maintains its VWF-like and kielin-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 45 percent of the residues may be so changed.

The protein similarity information, expression pattern, and map location for the VWF-like and kielin-like protein and nucleic acid (NOV3) disclosed herein suggest that NOV3 may have important structural and/or physiological functions characteristic of the VWF-like and kielin-like kinase-like family. Therefore, the NOV3 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications. These include

serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo.

The NOV3 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from cancer, inflammation, neurological disorders, neuropsychiatric disorders, obesity, diabetes, bleeding disorders and/or other pathologies. The NOV3 nucleic acid, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV3 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV3 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV3 epitope is from about amino acids 1 to 2. In another embodiment, a NOV3 epitope is from about amino acids 400 to 440. In additional embodiments, NOV3 epitopes are from about amino acids 900 to 950 and from about amino acids 1375 to 1425. This novel protein also has value in development of powerful assay system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV4

NOV4 includes six novel semaphorin-like proteins disclosed below. The disclosed sequences have been named NOV4a, NOV4b, NOV4c, NOV4d, NOV4e, and NOV4f.

NOV4a

A disclosed NOV4a nucleic acid of 1896 nucleotides (designated CuraGen Acc. No. SC70504370_A/CG59253-01) encoding a novel Sempahorin-like protein is shown in Table

4a. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 46-48 and ending with a TAG codon at nucleotides 1474-1476.

Table 4A. NOV4a Nucleotide Sequence (SEQ ID NO:9)

```
TGGCATTTCTGAGCAGGGGCCACCCTGACTTCACCTTGGCCCACCATGAGGGTCTTCCTGCTTTGTGCCT
ACATACTGCTGCTGATGGTTTCCCAGTTGAGGGCAGTCAGCTTTCCTGAAGATGATGAACCCCTTAATAC
TGTCGACTATCACTATTCAAGGCAATATCCGGTTTTTAGAGGACGCCCTTCAGGCAATGAATCGCAGCAC
AGGCTGGACTTTCAGCTGATGTTGAAAATTCGAGACACACTTTATATTGCTGGCAGGGATCAAGTTTATA
CAGTAAACTTAAATGAAATGCCCAAAACAGAAGTAATACCCAACAAGAAACTGACATGGCGATCAAGACA
ACAGGATCGAGAAAACTGTGCTATGAAAGGCAAGCATAAAGATGAATGCCACAACTTTATCAAAGTATTT
GTTCCAAGAAACGATGAGATGGTTTTTGTTTGTGGTACCAATGCATTCAATCCCATGTGTAGATACTACA
GGTTGAGTACCTTAGAATATGATGGGGAAGAAATTAGTGGCCTGGCAAGATGCCCATTTGATGCCAGACA
AACCAATGTTGCCCTCTTTGCTGATGGGAAGCTGTATTCTGCCACAGTGGCTGACTTCTTGGCCAGCGAT
GCCGTTATTTATCGAAGCATGGGTGATGGATCTGCCCTTCGCACAATAAAATATGATTCCAAATGGATAA
AAGAGCCACACTTTCTTCATGCCATAGAATATGGAAACTATGTCTATTTCTTCTTTCGAGAAATCGCTGT
CGAACATAATAATTTAGGCAAGGCTGTGTATTCCCGCGTGGCCCGCATATGTAAAAACGACATGGGTGGT
TCCCAGCGGGTCCTGGAGAAACACTGGACTTCATTTCTAAAGGCTCGGCTGAACTGTTCTGTCCCTGGAG
ATTCGTTTTTCTACTTTGATGTTCTGCAGTCTATTACAGACATAATACAAATCAATGGCATCCCCACTGT
GGTCGGGGTGTTTACCACGCAGCTCAATAGCATCCCTGGTTCTGCTGTCTGTGCATTTAGCATGGATGAC
ATTGAAAAAGTATTCAAAGGACGGTTTAAGGAACAGAAAACTCCAGATTCTGTTTGGACAGCAGTTCCCG
AAGACAAAGTGCCAAAGCCAAGGCCTGGCTGTTGTGCAAAACACGGCCTTGCCGAAGCTTATAAAACCTC
CATCGATTTCCCGGATGAAACTCTGTCATTCATCAAATCTCATCCCCTGATGGACTCTGCCGTTCCACCC
ATTGCCGATGAGCCCTGGTTCACAAAGACTCGGGTCAGGTACAGACTGACGGCCATCTCAGTGGACCATT
CAGCCGGACCCTACCAGAACTACACAGTCATCTTTGTTGGCTCTGAAGCTGGCATGGTACTTAAAGTTCT
GGCAAAGACCAGTCCTTTCTCTTTGAACGACAGCGTATTACTGGAAGAGATTGAAGCCTACAACCATGCA
AAGTAGGTATATGTTACGAGAACGCCCTTCAGCACTGCTCAAAAATTTTCGGCATGTATTTCATCTAGTC
ATGTCCTTTTGGTCCTCTAAATTAGCAGTGGTTTGGCATAATAGTGTTTTGTGTTTTTTTTCTCATTGAA
ATAAATCTTGGGTTTGTTTTTTTCCCGAGCCTGCTAGGGCGAGGGGGGTGAATGGTTGATGAGTTTAAAA
ATAATGCAGCCCTTGTTTTTCACCTGTAGAATATGAGAACATTTTAACAGCACCTCTCTTATCTTGCAGA
TATATTCCAAGATGCTACATGCAGCAGACAGCTGTGAGCTTGCATACACACACACACAAATATACATGCA
CATACATACACAGAATGCAGTACTAGTTAAGTATTTCCTTCCTATCTTTAATAAGTAAGAGAATATTTAG
ACCATT
```

A NOV4a nucleic acid is found in at least Brain (Hippocampus, Substantia Nigra), and Kidney. A NOV4a nucleic acid has 1588 of 1588 bases (100%) identical to a gb:GENBANK-ID:AK021660|acc:AK021660.1 mRNA from Homo sapiens (Homo sapiens cDNA FLJ11598 fis, clone HEMBA1003866, moderately similar to Mus musculus semaphorin VIa mRNA).

A NOV4a polypeptide (SEQ ID NO:16) encoded by SEQ ID NO:15 is 476 amino acid residues and is presented using the one letter code in Table 4B. Signal P, Psort and/or Hydropathy results predict that NOV4a has a signal peptide and is likely to be localized outside the cell with a certainty of 0.7380. In other embodiments, NOV4a may also be localized to the lysosome (lumen) with a certainty of 0.1900 or to the microbody with a certainty of 0.1875.

Table 4B. NOV4a protein sequence (SEQ ID NO:10)

```
MRVFLLCAYILLLMVSQLRAVSFPEDDEPLNTVDYHYSRQYPVFRGRPSGNESQHRLDFQLMLKIRDTLY
IAGRDQVYTVNLNEMPKTEVIPNKKLTWRSRQQDRENCAMKGKHKDECHNFIKVFVPRNDEMVFVCGTNA
FNPMCRYYRLSTLEYDGEEISGLARCPFDARQTNVALFADGKLYSATVADFLASDAVIYRSMGDGSALRT
IKYDSKWIKEPHFLHAIEYGNYVYFFFREIAVEHNNLGKAVYSRVARICKNDMGGSQRVLEKHWTSFLKA
RLNCSVPGDSFFYFDVLQSITDIIQINGIPTVVGVFTTQLNSIPGSAVCAFSMDDIEKVFKGRFKEQKTP
DSVWTAVPEDKVPKPRPGCCAKHGLAEAYKTSIDFPDETLSFIKSHPLMDSAVPPIADEPWFTKTRVRYR
LTAISVDHSAGPYQNYTVIFVGSEAGMVLKVLAKTSPFSLNDSVLLEEIEAYNHAK
```

The full amino acid sequence of the protein of the invention was found to have 367 of 367 amino acid residues (100%) identical to, and 367 of 367 amino acid residues (100%) similar to, the 367 amino acid residue ptnr:TREMBLNEW-ACC:BAB13869 protein from Homo sapiens (Human) (CDNA FLJ11598 FIS, CLONE HEMBA1003866, MODERATELY SIMILAR TO MUS MUSCULUS SEMAPHORIN VIA MRNA).

NOV4b

A disclosed NOV4b nucleic acid of 3025 nucleotides (designated CuraGen Acc. No. CG59253-02) encoding a novel semaphorin-like protein is shown in Table 4C. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 46-48 and ending with a TAG codon at nucleotides 3151-3153. Putative untranslated regions upstream of the initiation codon and downstream from the termination codon is underlined in Table 4C, and the start and stop codons are in bold letters.

Table 4C. NOV4b Nucleotide Sequence (SEQ ID NO:11)

TGGCATTTCTGAGCAGGGGCCACCCTGACTTCACCTTGGCCCACC**ATG**AGGGTCTTCCTG
CTTTGTGCCTACATACTGCTGCTGATGGTTTCCCAGTTGAGGGCAGTCAGCTTTCCTGAA
GATGATGAACCCCTTAATACTGTCGACTATCACTGTAAGTCGTCTAGGCAATATCCGGTT
TTTAGAGGACGCCCTTCAGGCAATGAATCGCAGCACAGGCTGGACTTTCAGCTGATGTTG
AAAATTCGAGACACACTTTATATTGCTGGCAGGGATCAAGTTTATACAGTAAACTTAAAT
GAAATGCCCAAAACAGAAGTAATATGGCAACAGAAACTGACATGGCGATCAAGACAACAG
GATCGAGAAAACTGTGCTATGAAAGGCAAGCATAAAGATGAATGCCACAACTTTATCAAA
GTATTTGTTCCAAGAAACGATGAGATGGTTTTTGTTTGTGGTACCAATGCATTCAATCCC
ATGTGTAGATACTACAGGGTAAGTACCTTAGAATATGATGGGGAAGAAATTAGTGGCCTG
GCAAGATGCCCATTTGATGCCAGACAAACCAATGTTGCCCTCTTTGCTGATGGGAAGCTG
TATTCTGCCACAGTGGCTGACTTCTTGGCCAGCGATGCCGTTATTTATCGAAGCATGGGT
GATGGATCTGCCCTTCGCACAATAAAATATGATTCCAAATGGATAAAAGAGCCACACTTT
CTTCATGCCATAGAATATGGAAACTATGTCTATTTCTTCTTTCGAGAAATCGCTGTCGAA
CATAATAATTTAGGCAAGGCTGTGTATTCCCGCGTGGCCCGCATATGTAAAAACGACATG
GGTGGTTCCCAGCGGGTCCTGGAGAAACACTGGACTTCATTTCTAAAGGCTCGGCTGAAC
TGTTCTGTCCCTGGAGATTCGTTTTTCTACTTTGATGTTCTGCAGTCTATTACAGACATA
ATACAAATCAATGGCATCCCCACTGTGGTCGGGGTGTTTACCACGCAGCTCAATAGCATC
CCTGGTTCTGCTGTCTGTGCATTTAGCATGGATGACATTGAAAAAGTATTCAAAGGACGG
TTTAAGGAACAGAAAACTCCAGATTCTGTTTGGACAGCAGTTCCCGAAGACAAAGTGCCA
AAGCCAAGGCCTGGCTGTTGTGCAAAACACGGCCTTGCCGAAGCTTATAAAACCTCCATC
GATTTCCCGGATGAAACTCTGTCATTCATCAAATCTCATCCCCTGATGGACTCTGCCGTT
CCACCCATTGCCGATGAGCCCTGGTTCACAAAGACTCGGGTCAGGTACAGACTGACGGCC
ATCTCAGTGGACCATTCAGCCGGACCCTACCAGAACTACACAGTCATCTTTGTTGGCTCT
GAAGCTGGCATGGTACTTAAAGTTCTGGCAAAGACCAGTCCTTTCTCTTTGAACGACAGC
GTATTACTGGAAGAGATTGAAGCCTACAACCATGCAAAGTGCAGTGCTGAGAATGAGGAA
GACAAAAAGGTCATCTCATTACAGTTGGATAAAGATCACCACGCTTTATATGTGGCGTTC
TCTAGCTGCATTATCCGCATCCCCCTCAGTCGCTGTGAGCGTTATGGATCATGTAAAAAG
TCTTGTATTGCATCTCGTGACCCGTATTGTGGCTGGTTAAGCCAGGGATCCTGTGGTAGA
GTGACCCCAAACCACAGTGCTGAAGGATATGAACAAGACACAGAATTCGGCAACACAGCT
CATCTAGGGGACTGCCATGCATATGAACCATATGAAGGTCGTGTTGGCTCACTGAAAGCC
ATTTGCTATTTATTATTATTTTTTAAAAAGCACCTTATTCACATTGTCCCATGTGTCTATT
TCAGGTGTACGATGGGAAGTCCAGTCTGGAGAGTCCAACCAGATGGTCCACATGAATGTC
CTCATCACCTGTGTCTTTGCTGCTTTTGTTTTGGGGGCATTCATTGCAGGTGTGGCAGTA
TACTGCTATCGAGACATGTTTGTTCGGAAAAACAGAAAGATCCATAAAGATGCAGAGTCC
GCCCAGTCATGCACAGACTCCAGTGGAAGTTTTGCCAAACTGAATGGTCTCTTTGACAGC
CCTGTCAAGGAATACCAACAGAATATTGATTCTCCTAAACTGTATAGTAACCTGCTAACC

AGTCGGAAAGAGCTACCACCCAATGGAGATACTAAATCCATGGTAATGGACCATCGAGGG
CAACCTCCAGAGTTGGCTGCTCTTCCTACTCCTGAGTCTACACCCGTGCTTCACCAGAAG
ACCCTGCAGGCCATGAAGAGCCACTCAGAAAAGGCCCATGGCCATGGAGCTTCAAGGAAA
GAAACCCCTCAGTTTTTTCCGTCTAGTCCGCCACCTCATTCCCCATTAAGTCATGGGCAT
ATCCCCAGTGCCATTGTTCTTCCAAATGCTACCCATGACTACAACACGTCTTTCTCAAAC
TCCAATGCTCACAAAGCTGAAAAGAAGCTTCAAAACATTGATCACCCTCTCACAAAGTCA
TCCAGTAAGAGAGATCACCGGCGTTCTGTTGATTCCAGAAATACCCTCAATGATCTCCTG
AAGCATCTGAATGACCCAAATAGTAACCCCAAAGCCATCATGGGAGACATCCAGATGGCA
CACCAGAACTTAATGCTGGATCCCATGGGATCGATGTCTGAGGTCCCACCTAAAGTCCCT
AACCGGGAGGCATCGCTATACTCCCCTCCTTCAACTCTCCCCAGAAATAGCCCAACCAAG
CGAGTGGATGTCCCCACCACTCCTGGAGTCCCAATGACTTCTCTGGAAAGACAAAGAGGT
TATCACAAAAATTCCTCCCAGAGGCACTCTATATCTGCTATGCCTAAAAACTTAAACTCA
CCAAATGGTGTTTTGTTATCCAGACAGCCTAGTATGAACCGTGGAGGATATATGCCCACC
CCCACTGGGGCGAAGGTGGACTATATTCAGGGAACACCAGTGAGTGTTCATCTGCAGCCT
TCCCTCTCCAGACAGAGCAGCTACACCAGTAATGGCACTCTTCCTAGGACGGGACTAAAG
AGGACGCCGTCCTTAAAACCTGACGTGCCACCAAAGCCTTCCTTTGTTCCTCAAACCCCA
TCTGTCAGACCACTGAACAAATACACATAC**TAG**GCCTCAAGTGTGCTATTCCCATGTGGC
TTTATCCTGTCCGTGTTGTTGAGAG

The nucleic acid sequence of NOV4b maps to chromosome 15q21.1 and has 1134 of 1656 bases (68%) identical to a mouse semaphorin IV mRNA (Accession No. AF030430) (E = $1.0e^{-132}$).

A NOV4b polypeptide (SEQ ID NO:18) encoded by SEQ ID NO:17 is 1035 amino acid residues and is presented using the one letter code in Table 4D. Signal P, Psort and/or Hydropathy results predict that NOV4b has a signal peptide and is likely to be localized at the plasma membrane with a certainty of 0.4600. In other embodiments, NOV4b may also be localized to the endoplasmic reticulum (membrane or lumen) with a certainty of 0.1000, or outside the cell with a certainty of 0.1000. The most likely cleavage site is between positions 20 and 21 (LRA-VS).

Table 4D. NOV4b protein sequence (SEQ ID NO:12)

MRVFLLCAYILLLMVSQLRAVSFPEDDEPLNTVDYHCKSSRQYPVFRGRPSGNESQHRLD
FQLMLKIRDTLYIAGRDQVYTVNLNEMPKTEVIWQQKLTWRSRQQDRENCAMKGKHKDEC
HNFIKVFVPRNDEMVFVCGTNAFNPMCRYYRVSTLEYDGEEISGLARCPFDARQTNVALF
ADGKLYSATVADFLASDAVIYRSMGDGSALRTIKYDSKWIKEPHFLHAIEYGNYVYFFFR
EIAVEHNNLGKAVYSRVARICKNDMGGSQRVLEKHWTSFLKARLNCSVPGDSFFYFDVLQ
SITDIIQINGIPTVVGVFTTQLNSIPGSAVCAFSMDDIEKVFKGRFKEQKTPDSVWTAVP
EDKVPKPRPGCCAKHGLAEAYKTSIDFPDETLSFIKSHPLMDSAVPPIADEPWFTKTRVR
YRLTAISVDHSAGPYQNYTVIFVGSEAGMVLKVLAKTSPFSLNDSVLLEEIEAYNHAKCS
AENEEDKKVISLQLDKDHHALYVAFSSCIIRIPLSRCERYGSCKKSCIASRDPYCGWLSQ
GSCGRVTPNHSAEGYEQDTEFGNTAHLGDCHAYEPYEGRVGSLKAICYLLLFLKSTLFTL
SHVSISGVRWEVQSGESNQMVHMNVLITCVFAAFVLGAFIAGVAVYCYRDMFVRKNRKIH
KDAESAQSCTDSSGSFAKLNGLFDSPVKEYQQNIDSPKLYSNLLTSRKELPPNGDTKSMV
MDHRGQPPELAALPTPESTPVLHQKTLQAMKSHSEKAHGHGASRKETPQFFPSSPPPHSP
LSHGHIPSAIVLPNATHDYNTSFSNSNAHKAEKKLQNIDHPLTKSSSKRDHRRSVDSRNT
LNDLLKHLNDPNSNPKAIMGDIQMAHQNLMLDPMGSMSEVPPKVPNREASLYSPPSTLPR
NSPTKRVDVPTTPGVPMTSLERQRGYHKNSSQRHSISAMPKNLNSPNGVLLSRQPSMNRG
GYMPTPTGAKVDYIQGTPVSVHLQPSLSRQSSYTSNGTLPRTGLKRTPSLKPDVPPKPSF
VPQTPSVRPLNKYTY

The full amino acid sequence of the protein of the invention was found to have 354 of 583 amino acid residues (60%) identical to, and 448 of 583 amino acid residues (76%) similar

to, the 1030 amino acid residue ptnr:TREMBLNEW-ACC:Q9H2E6 semaphorein 6A1 protein from *Homo sapiens* ($E = 1.1e^{-222}$).

NOV4b is expressed in at least the following tissues: dipose, heart, pancreas, thyroid, liver, gall bladder, colon, brain, right cerebellum, left cerebellum, thalamus, hypothalamus, frontal lobe, parietal lobe, cerebral medulla/cerebral white matter, substantia nigra, hippocampus, spinal cord, peripheral nerves, mammary gland/breast, ovary, placenta, lung, kidney, skin, foreskin, and epidermis. Expression information was derived from the tissue sources of the sequences that were included in the derivation of the sequence of CuraGen Acc. No. CG59253-01.

NOV4c

A disclosed NOV4c nucleic acid of 2191 nucleotides (designated CuraGen Acc. No. CG59253-05) encoding a novel semaphorin-like protein is shown in Table 4E. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 46-48 and ending with a TAG codon at nucleotides 2182-2184. Putative untranslated regions upstream of the initiation codon and downstream from the termination codon is underlined in Table 4E, and the start and stop codons are in bold letters.

Table 4E. NOV4c Nucleotide Sequence (SEQ ID NO:13)

TGGCATTTCTGAGCAGGGGCCACCCTGACTTCACCTTGGCCCACC**ATG**AGGGTCTTCCTG
CTTTGTGCCTACATACTGCTGCTGATGGTTTCCCAGTTGAGGGCAGTCAGCTTTCCTGAA
GATGATGAACCCCTTAATACTGTCGACTATCACTGTAAGTCGTCTAGGCAATATCCGGTT
TTTAGAGGACGCCCTTCAGGCAATGAATCGCAGCACAGGCTGGACTTTCAGCTGATGTTG
AAAATTCGAGACACACTTTATATTGCTGGCAGGGATCAAGTTTATACAGTAAACTTAAAT
GAAATGCCCAAAACAGAAGTAATATGGCAACAGAAACTGACATGGCGATCAAGACAACAG
GATCGAGAAAACTGTGCTATGAAAGGCAAGCATAAAGATGAATGCCACAACTTTATCAAA
GTATTTGTTCCAAGAAACGATGAGATGGTTTTTGTTTGTGGTACCAATGCATTCAATCCC
ATGTGTAGATACTACAGGGTAAGTACCTTAGAATATGATGGGGAAGAAATTAGTGGCCTG
GCAAGATGCCCATTTGATGCCAGACAAACCAATGTTGCCCTCTTTGCTGATGGGAAGCTG
TATTCTGCCACAGTGGCTGACTTCTTGGCCAGCGATGCCGTTATTTATCGAAGCATGGGT
GATGGATCTGCCCTTCGCACAATAAAATATGATTCCAAATGGATAAAAGAGCCACACTTT
CTTCATGCCATAGAATATGGAAACTATGTCTATTTCTTCTTTCGAGAAATCGCTGTCGAA
CATAATAATTTAGGCAAGGCTGTGTATTCCCGCGTGGCCCGCATATGTAAAAACGACATG
GGTGGTTCCCAGCGGGTCCTGGAGAAACACTGGACTTCATTTCTAAAGGCTCGGCTGAAC
TGTTCTGTCCCTGGAGATTCGTTTTTCTACTTTGATGTTCTGCAGTCTATTACAGACATA
ATACAAATCAATGGCATCCCCACTGTGGTCGGGGTGTTTACCACGCAGCTCAATAGCATC
CCTGGTTCTGCTGTCTGTGCATTTAGCATGGATGACATTGAAAAAGTATTCAAAGGACGG
TTTAAGGAACAGAAAACTCCAGATTCTGTTTGGACAGCAGTTCCCGAAGACAAAGTGCCA
AAGCCAAGGCCTGGCTGTTGTGCAAAACACGGCCTTGCCGAAGCTTATAAAACCTCCATC
GATTTCCCGGATGAAACTCTGTCATTCATCAAATCTCATCCCCTGATGGACTCTGCCGTT
CCACCCATTGCCGATGAGCCCTGGTTCACAAAGACTCGGGTCAGGTACAGACTGACGGCC
ATCTCAGTGGACCATTCAGCCGGACCCTACCAGAACTACACAGTCATCTTTGTTGGCTCT
GAAGCTGGCATGGTACTTAAAGTTCTGGCAAAGACCAGTCCTTTCTCTTTGAACGACAGC
GTATTACTGGAAGAGATTGAAGCCTACAACCATGCAAAGTGCAGTGCTGAGAATGAGGAA
GACAAAAAGGTCATCTCATTACAGTTGGATAAAGATCACCACGCTTTATATGTGGCGTTC
TCTAGCTGCATTATCCGCATCCCCCTCAGTCGCTGTGAGCGTTATGGATCATGTAAAAAG
TCTTGTATTGCATCTCGTGACCCGTATTGTGGCTGGTTAAGCCAGGGATCCTGTGGTAGA
GTGACCCCAGGGATGCTGCTGTTAACCGAAGACTTCTTTGCTTTCCATAACCACAGTGCT
GAAGGATATGAACAAGACACAGAATTCGGCAACACAGCTCATCTAGGGGACTGCCATGAA
ATTTTGCCTACTTCAACTACACCAGATTACAAAATATTTGGCGGTCCAACATCTGGTGTA

CGATGGGAAGTCCAGTCTGGAGAGTCCAACCAGATGGTCCACATGAATGTCCTCATCACC
TGTGTCTTTGCTGCTTTTGTTTTGGGGGCATTCATTGCAGGTGTGGCAGTATACTGCTAT
CGAGACATGTTTGTTCGGAAAAACAGAAAGATCCATAAAGATGCAGAGTCCGCCCAGTCA
TGCACAGACTCCAGTGGAAGTTTTGCCAAACTGAATGGTCTCTTTGACAGCCCTGTCAAG
GAATACCAACAGAATATTGATTCTCCTAAACTGTATAGTAACCTGCTAACCAGTCGGAAA
GAGCACGAATTCAGCGGCCGC**TGA**ATTCTAG

The nucleic acid sequence of NOV4c maps to chromosome 15 and has 1161 of 1166 bases (99%) identical to a gb:GENBANK-ID:AK021660|acc:AK021660.1 mRNA from Homo sapiens (Homo sapiens cDNA FLJ11598 fis, clone HEMBA1003866, moderately similar to Mus musculus semaphorin VIa mRNA).

A NOV4c polypeptide (SEQ ID NO:18) encoded by SEQ ID NO:17 is 712 amino acid residues and is presented using the one letter code in Table 4D. Signal P, Psort and/or Hydropathy results predict that NOV4c has a signal peptide and is likely to be localized at the plasma membrane with a certainty of 0.4600. In other embodiments, NOV4c may also be localized to the microbody with a certainty of -.1812, or to the endoplasmic reticulum (membrane or lumen) with a certainty of 0.1000. The most likely cleavage site is between positions 20 and 21 (LRA-VS).

Table 4F. NOV4c protein sequence (SEQ ID NO:14)

MRVFLLCAYILLLMVSQLRAVSFPEDDEPLNTVDYHCKSSRQYPVFRGRPSGNESQHRLD
FQLMLKIRDTLYIAGRDQVYTVNLNEMPKTEVIWQQKLTWRSRQQDRENCAMKGKHKDEC
HNFIKVFVPRNDEMVFVCGTNAFNPMCRYYRVSTLEYDGEEISGLARCPFDARQTNVALF
ADGKLYSATVADFLASDAVIYRSMGDGSALRTIKYDSKWIKEPHFLHAIEYGNYVYFFFR
EIAVEHNNLGKAVYSRVARICKNDMGGSQRVLEKHWTSFLKARLNCSVPGDSFFYFDVLQ
SITDIIQINGIPTVVGVFTTQLNSIPGSAVCAFSMDDIEKVFKGRFKEQKTPDSVWTAVP
EDKVPKPRPGCCAKHGLAEAYKTSIDFPDETLSFIKSHPLMDSAVPPIADEPWFTKTRVR
YRLTAISVDHSAGPYQNYTVIFVGSEAGMVLKVLAKTSPFSLNDSVLLEEIEAYNHAKCS
AENEEDKKVISLQLDKDHHALYVAFSSCIIRIPLSRCERYGSCKKSCIASRDPYCGWLSQ
GSCGRVTPGMLLLTEDFFAFHNHSAEGYEQDTEFGNTAHLGDCHEILPTSTTPDYKIFGG
PTSGVRWEVQSGESNQMVHMNVLITCVFAAFVLGAFIAGVAVYCYRDMFVRKNRKIHKDA
ESAQSCTDSSGSFAKLNGLFDSPVKEYQQNIDSPKLYSNLLTSRKEHEFSGR

The full amino acid sequence of the protein of the invention was found to have 577 of 586 amino acid residues (98%) identical to, and 580 of 586 amino acid residues (98%) similar to, the 1022 amino acid residue ptnr:TREMBLNEW-ACC:BAA96003 protein from Homo sapiens (Human) (KIAA1479 PROTEIN).

NOV4c is expressed in at least the following tissues: whole embryo, mainly head and neck.

NOV4d

A disclosed NOV4d nucleic acid of 3196 nucleotides (designated CuraGen Acc. No. CG59253-06) encoding a novel semaphorin-like protein is shown in Table 4E. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 46-48 and ending at nucleotides 3142-3144. Putative untranslated regions upstream of the initiation codon and downstream from the termination codon is underlined in Table 4E, and the start and stop codons are in bold letters.

Table 4G. NOV4d Nucleotide Sequence (SEQ ID NO:15)

TGGCATTTCTGAGCAGGGGCCACCCTGACTTCACCTTGGCCCACC**ATG**AGGGTCTTCCTG
CTTTGTGCCTACATACTGCTGCTGATGGTTTCCCAGTTGAGGGCAGTCAGCTTTCCTGAA
GATGATGAACCCCTTAATACTGTCGACTATCACTGTAAGTCGTCTAGGCAATATCCGGTT
TTTAGAGGACGCCCTTCAGGCAATGAATCGCAGCACAGGCTGGACTTTCAGCTGATGTTG
AAAATTCGAGACACACTTTATATTGCTGGCAGGGATCAAGTTTATACAGTAAACTTAAAT
GAAATGCCCAAAACAGAAGTAATATGGCAACAGAAACTGACATGGCGATCAAGACAACAG
GATCGAGAAAACTGTGCTATGAAAGGCAAGCATAAAGATGAATGCCACAACTTTATCAAA
GTATTTGTTCCAAGAAACGATGAGATGGTTTTTGTTTGTGGTACCAATGCATTCAATCCC
ATGTGTAGATACTACAGGGTAAGTACCTTAGAATATGATGGGGAAGAAATTAGTGGCCTG
GCAAGATGCCCATTTGATGCCAGACAAACCAATGTTGCCCTCTTTGCTGATGGGAAGCTG
TATTCTGCCACAGTGGCTGACTTCTTGGCCAGCGATGCCGTTATTTATCGAAGCATGGGT
GATGGATCTGCCCTTCGCACAATAAAATATGATTCCAAATGGATAAAAGAGCCACACTTT
CTTCATGCCATAGAATATGGAAACTATGTCTATTTCTTCTTTCGAGAAATCGCTGTCGAA
CATAATAATTTAGGCAAGGCTGTGTATTCCCGCGTGGCCCGCATATGTAAAAACGACATG
GGTGGTTCCCAGCGGGTCCTGGAGAAACACTGGACTTCATTTCTAAAGGCTCGGCTGAAC
TGTTCTGTCCCTGGAGATTCGTTTTTCTACTTTGATGTTCTGCAGTCTATTACAGACATA
ATACAAATCAATGGCATCCCCACTGTGGTCGGGGTGTTTACCACGCAGCTCAATAGCATC
CCTGGTTCTGCTGTCTGTGCATTTAGCATGGATGACATTGAAAAAGTATTCAAAGGACGG
TTTAAGGAACAGAAAACTCCAGATTCTGTTTGGACAGCAGTTCCCGAAGACAAAGTGCCA
AAGCCAAGGCCTGGCTGTTGTGCAAAACACGGCCTTGCCGAAGCTTATAAAACCTCCATC
GATTTCCCGGATGAAACTCTGTCATTCATCAAATCTCATCCCCTGATGGACTCTGCCGTT
CCACCCATTGCCGATGAGCCCTGGTTCACAAAGACTCGGGTCAGGTACAGACTGACGGCC
ATCTCAGTGGACCATTCAGCCGGACCCTACCAGAACTACACAGTCATCTTTGTTGGCTCT
GAAGCTGGCATGGTACTTAAAGTTCTGGCAAAGACCAGTCCTTTCTCTTTGAACGACAGC
GTATTACTGGAAGAGATTGAAGCCTACAACCATGCAAAGTGCAGTGCTGAGAATGAGGAA
GACAAAAAGGTCATCTCATTACAGTTGGATAAAGATCACCACGCTTTATATGTGGCGTTC
TCTAGCTGCATTATCCGCATCCCCCTCAGTCGCTGTGAGCGTTATGGATCATGTAAAAAG
TCTTGTATTGCATCTCGTGACCCGTATTGTGGCTGGTTAAGCCAGGGATCCTGTGGTAGA
GTGACCCCAGGGATGCTGCTGTTAACCGAAGACTTCTTTGCTTTCCATAACCACAGTGCT
GAAGGATATGAACAAGACACAGAATTCGGCAACACAGCTCATCTAGGGGACTGCCATGAA
ATTTTGCCTACTTCAACTACACCAGATTACAAAATATTTGGCGGTCCAACATCTGGTGTA
CGATGGGAAGTCCAGTCTGGAGAGTCCAACCAGATGGTCCACATGAATGTCCTCATCACC
TGTGTCTTTGCTGCTTTTGTTTTGGGGGCATTCATTGCAGGTGTGGCAGTATACTGCTAT
CGAGACATGTTTGTTCGGAAAAACAGAAAGATCCATAAAGATGCAGAGTCCGCCCAGTCA
TGCACAGACTCCAGTGGAAGTTTTGCCAAACTGAATGGTCTCTTTGACAGCCCTGTCAAG
GAATACCAACAGAATATTGATTCTCCTAAACTGTATAGTAACCTGCTAACCAGTCGGAAA
GAGCTACCACCCAATGGAGATTCTAAATCCATGGTAATGGACCATCGAGGGCAACCTCCA
GAGTTGGCTGCTCTTCCTACTCCTGAGTCTACACCCGTGCTTCACCAGAAGACCCTGCAG
GCCATGAAGAGCCACTCAGAAAAGGCCCATGGCCATGGAGCTTCAAGGAAAGAAACCCCT
CAGTTTTTTCCGTCTAGTCCGCCACCTCATTCCCCATTAAGTCATGGGCATATCCCCAGT
GCCATTGTTCTTCCAAATGCTACCCATGACTACAACACGTCTTTCTCAAACTCCAATGCT
CACAAAGCTGAAAAGAAGCTTCAAAACATTGATCACCCTCTCACAAAGTCATCCAGTAAG
AGAGATCACCGGCGTTCTGTTGATTCCAGAAATACCCTCAATGATCTCCTGAAGCATCTG
AATGACCCAAATAGTAACCCCAAAGCCATCATGGGAGACATCCAGATGGCACACCAGAAC
TTAATGCTGGATCCCATGGGATCGATGTCTGAGGTCCCACCTAAAGTCCCTAACCGGGAG
GCATCGCTATACTCCCCTCCTTCAACTCTCCCCAGAAATAGCCCAACCAAGCGAGTGGAT
GTCCCCACCACTCCTGGAGTCCCAATGACTTCTCTGGAAAGACAAAGAGGTTATCACAAA
AATTCCTCCCAGAGGCACTCTATATCTGCTATGCCTAAAAACTTAAACTCACCAAATGGT
GTTTTGTTATCCAGACAGCCTAGTATGAACCGTGGAGGATATATGCCCACCCCCACTGGG
GCGAAGGTGGACTATATTCAGGGAACACCAGTGAGTGTTCATCTGCAGCCTTCCCTCTCC
AGACAGAGCAGCTACACCAGTAATGGCACTCTTCCTAGGACGGGACTAAAGAGGACGCCG
TCCTTAAAACCTGACGTGCCACCAAAGCCTTCCTTTGTTCCTCAAACCCCATCTGTCAGA
CCACTGAACAAATACACATAC**TAG**GCCTCAAGTGTGCTATTCCCATGTGGCTTTATCCTG

TCCGTGTTGTTGAGAG

The nucleic acid sequence of NOV4d maps to chromosome 15 and has 1786 of 1798 bases (99%) identical to a gb:GENBANK-ID:AB040912|acc:AB040912.2 mRNA from Homo sapiens (Homo sapiens mRNA for KIAA1479 protein, partial cds).

A NOV4d polypeptide (SEQ ID NO:18) encoded by SEQ ID NO:17 is 1032 amino acid residues and is presented using the one letter code in Table 4D.

Table 4H. NOV4d protein sequence (SEQ ID NO:16)

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MRVFLLCAYILLLMVSQLRAVSFPEDDEPLNTVDYHCKSSRQYPVFRGRPSGNESQHRLD
FQLMLKIRDTLYIAGRDQVYTVNLNEMPKTEVIWQQKLTWRSRQQDRENCAMKGKHKDEC
HNFIKVFVPRNDEMVFVCGTNAFNPMCRYYRVSTLEYDGEEISGLARCPFDARQTNVALF
ADGKLYSATVADFLASDAVIYRSMGDGSALRTIKYDSKWIKEPHFLHAIEYGNYVYFFFR
EIAVEHNNLGKAVYSRVARICKNDMGGSQRVLEKHWTSFLKARLNCSVPGDSFFYFDVLQ
SITDIIQINGIPTVVGVFTTQLNSIPGSAVCAFSMDDIEKVFKGRFKEQKTPDSVWTAVP
EDKVPKPRPGCCAKHGLAEAYKTSIDFPDETLSFIKSHPLMDSAVPPIADEPWFTKTRVR
YRLTAISVDHSAGPYQNYTVIFVGSEAGMVLKVLAKTSPFSLNDSVLLEEIEAYNHAKCS
AENEEDKKVISLQLDKDHHALYVAFSSCIIRIPLSRCERYGSCKKSCIASRDPYCGWLSQ
GSCGRVTPGMLLLTEDFFAFHNHSAEGYEQDTEFGNTAHLGDCHEILPTSTTPDYKIFGG
PTSGVRWEVQSGESNQMVHMNVLITCVFAAFVLGAFIAGVAVYCYRDMFVRKNRKIHKDA
ESAQSCTDSSGSFAKLNGLFDSPVKEYQQNIDSPKLYSNLLTSRKELPPNGDSKSMVMDH
RGQPPELAALPTPESTPVLHQKTLQAMKSHSEKAHGHGASRKETPQFFPSSPPPHSPLSH
GHIPSAIVLPNATHDYNTSFSNSNAHKAEKKLQNIDHPLTKSSSKRDHRRSVDSRNTLND
LLKHLNDPNSNPKAIMGDIQMAHQNLMLDPMGSMSEVPPKVPNREASLYSPPSTLPRNSP
TKRVDVPTTPGVPMTSLERQRGYHKNSSQRHSISAMPKNLNSPNGVLLSRQPSMNRGGYM
PTPTGAKVDYIQGTPVSVHLQPSLSRQSSYTSNGTLPRTGLKRTPSLKPDVPPKPSFVPQ
TPSVRPLNKYTY
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The full amino acid sequence of the disclosed NOV4e protein was found to have 577 of 586 amino acid residues (98%) identical to, and 580 of 586 amino acid residues (98%) similar to, the 1022 amino acid residue ptnr:TREMBLNEW-ACC:BAA96003 protein from Homo sapiens (Human) (KIAA1479 PROTEIN).

NOV4e

A disclosed NOV4e nucleic acid of 2359 nucleotides (designated CuraGen Acc. No. CG59253-07) encoding a novel semaphorin-like protein is shown in Table 4E. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 46-48 and ending at nucleotides 2350-2352. Putative untranslated regions upstream of the initiation codon and downstream from the termination codon is underlined in Table 4E, and the start and stop codons are in bold letters.

Table 4I. NOV4e Nucleotide Sequence (SEQ ID NO:17)

TGGCATTTCTGAGCAGGGGCCACCCTGACTTCACCTTGGCCCACC**ATG**AGGGTCTTCCTG
CTTTGTGCCTACATACTGCTGCTGATGGTTTCCCAGTTGAGGGCAGTCAGCTTTCCTGAA
GATGATGAACCCCTTAATACTGTCGACTATCACTGTAAGTCGTCTAGGCAATATCCGGTT
TTTAGAGGACGCCCTTCAGGCAATGAATCGCAGCACAGGCTGGACTTTCAGCTGATGTTG
AAAATTCGAGACACACTTTATATTGCTGGCAGGGATCAAGTTTATACAGTAAACTTAAAT
GAAATGCCCAAAACAGAAGTAATATGGCAACAGAAACTGACATGGCGATCAAGACAACAG
GATCGAGAAAACTGTGCTATGAAAGGCAAGCATAAAGATGAATGCCACAACTTTATCAAA
GTATTTGTTCCAAGAAACGATGAGATGGTTTTTGTTTGTGGTACCAATGCATTCAATCCC
ATGTGTAGATACTACAGGGTAAGTACCTTAGAATATGATGGGGAAGAAATTAGTGGCCTG
GCAAGATGCCCATTTGATGCCAGACAAACCAATGTTGCCCTCTTTGCTGATGGGAAGCTG
TATTCTGCCACAGTGGCTGACTTCTTGGCCAGCGATGCCGTTATTTATCGAAGCATGGGT
GATGGATCTGCCCTTCGCACAATAAAATATGATTCCAAATGGATAAAAGAGCCACACTTT
CTTCATGCCATAGAATATGGAAACTATGTCTATTTCTTCTTTCGAGAAATCGCTGTCGAA
CATAATAATTTAGGCAAGGCTGTGTATTCCCGCGTGGCCCGCATATGTAAAAACGACATG
GGTGGTTCCCAGCGGGTCCTGGAGAAACACTGGACTTCATTTCTAAAGGCTCGGCTGAAC
TGTTCTGTCCCTGGAGATTCGTTTTTCTACTTTGATGTTCTGCAGTCTATTACAGACATA
ATACAAATCAATGGCATCCCCACTGTGGTCGGGGTGTTTACCACGCAGCTCAATAGCATC
CCTGGTTCTGCTGTCTGTGCATTTAGCATGGATGACATTGAAAAAGTATTCAAAGGACGG
TTTAAGGAACAGAAAACTCCAGATTCTGTTTGGACAGCAGTTCCCGAAGACAAAGTGCCA
AAGCCAAGGCCTGGCTGTTGTGCAAAACACGGCCTTGCCGAAGCTTATAAAACCTCCATC
GATTTCCCGGATGAAACTCTGTCATTCATCAAATCTCATCCCCTGATGGACTCTGCCGTT
CCACCCATTGCCGATGAGCCCTGGTTCACAAAGACTCGGGTCAGGTACAGACTGACGGCC
ATCTCAGTGGACCATTCAGCCGGACCCTACCAGAACTACACAGTCATCTTTGTTGGCTCT
GAAGCTGGCATGGTACTTAAAGTTCTGGCAAAGACCAGTCCTTTCTCTTTGAACGACAGC
GTATTACTGGAAGAGATTGAAGCCTACAACCATGCAAAGTGCAGTGCTGAGAATGAGGAA
GACAAAAAGGTCATCTCATTACAGTTGGATAAAGATCACCACGCTTTATATGTGGCGTTC
TCTAGCTGCATTATCCGCATCCCCCTCAGTCGCTGTGAGCGTTATGGATCATGTAAAAAG
TCTTGTATTGCATCTCGTGACCCGTATTGTGGCTGGTTAAGCCAGGGATCCTGTGGTAGA
GTGACCCCAGGGATGCTGCTGTTAACCGAAGACTTCTTTGCTTTCCATAACCACAGTGCT
GAAGGATATGAACAAGACACAGAATTCGGCAACACAGCTCATCTAGGGGACTGCCATGAA
ATTTTGCCTACTTCAACTACACCAGATTACAAAATATTTGGCGGTCCAACATCTGACATG
GAGGTATCTTCATCTTCTGTTACCACAATGGCAAGTATCCCAGAAATCACACCTAAAGTG
ATTGATACCTGGAGACCTAAACTGACAAGCTCTCGGAAATTTGTAGTTCAAGATGATCCA
AACACTTCTGATTTTACTGATCCTTTATCGGGTATCCCAAAGGGTGTACGATGGGAAGTC
CAGTCTGGAGAGTCCAACCAGATGGTCCACATGAATGTCCTCATCACCTGTGTCTTTGCT
GCTTTTGTTTTGGGGGCATTCATTGCAGGTGTGGCAGTATACTGCTATCGAGACATGTTT
GTTCGGAAAAACAGAAAGATCCATAAAGATGCAGAGTCCGCCCAGTCATGCACAGACTCC
AGTGGAAGTTTTGCCAAACTGAATGGTCTCTTTGACAGCCCTGTCAAGGAATACCAACAG
AATATTGATTCTCCTAAACTGTATAGTAACCTGCTAACCAGTCGGAAAGAGCACGAATTC
AGCGGCCGC**TGA**ATTCTAG

The nucleic acid sequence of NOV4e maps to chromosome 15.

A NOV4e polypeptide (SEQ ID NO:18) encoded by SEQ ID NO:17 is 768 amino acid residues and is presented using the one letter code in Table 4e.

Table 4J. NOV4e protein sequence (SEQ ID NO:18)

MRVFLLCAYILLLMVSQLRAVSFPEDDEPLNTVDYHCKSSRQYPVFRGRPSGNESQHRLD
FQLMLKIRDTLYIAGRDQVYTVNLNEMPKTEVIWQQKLTWRSRQQDRENCAMKGKHKDEC
HNFIKVFVPRNDEMVFVCGTNAFNPMCRYYRVSTLEYDGEEISGLARCPFDARQTNVALF
ADGKLYSATVADFLASDAVIYRSMGDGSALRTIKYDSKWIKEPHFLHAIEYGNYVYFFFR
EIAVEHNNLGKAVYSRVARICKNDMGGSQRVLEKHWTSFLKARLNCSVPGDSFFYFDVLQ
SITDIIQINGIPTVVGVFTTQLNSIPGSAVCAFSMDDIEKVFKGRFKEQKTPDSVWTAVP
EDKVPKPRPGCCAKHGLAEAYKTSIDFPDETLSFIKSHPLMDSAVPPIADEPWFTKTRVR
YRLTAISVDHSAGPYQNYTVIFVGSEAGMVLKVLAKTSPFSLNDSVLLEEIEAYNHAKCS
AENEEDKKVISLQLDKDHHALYVAFSSCIIRIPLSRCERYGSCKKSCIASRDPYCGWLSQ
GSCGRVTPGMLLLTEDFFAFHNHSAEGYEQDTEFGNTAHLGDCHEILPTSTTPDYKIFGG
PTSDMEVSSSSVTTMASIPEITPKVIDTWRPKLTSSRKFVVQDDPNTSDFTDPLSGIPKG
VRWEVQSGESNQMVHMNVLITCVFAAFVLGAFIAGVAVYCYRDMFVRKNRKIHKDAESAQ
SCTDSSGSFAKLNGLFDSPVKEYQQNIDSPKLYSNLLTSRKEHEFSGR

NOV4f

A disclosed NOV4f nucleic acid of 3364 nucleotides (designated CuraGen Acc. No. CG59253-08) encoding a novel semaphorin-like protein is shown in Table 4f. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 46-48 and ending at nucleotides 3310-3312. Putative untranslated regions upstream of the initiation codon and downstream from the termination codon is underlined in Table 4f, and the start and stop codons are in bold letters.

Table 4K. NOV4f Nucleotide Sequence (SEQ ID NO:19)

TGGCATTTCTGAGCAGGGGCCACCCTGACTTCACCTTGGCCCACC**ATG**AGGGTCTTCCTG
CTTTGTGCCTACATACTGCTGCTGATGGTTTCCCAGTTGAGGGCAGTCAGCTTTCCTGAA
GATGATGAACCCCTTAATACTGTCGACTATCACTGTAAGTCGTCTAGGCAATATCCGGTT
TTTAGAGGACGCCCTTCAGGCAATGAATCGCAGCACAGGCTGGACTTTCAGCTGATGTTG
AAAATTCGAGACACACTTTATATTGCTGGCAGGGATCAAGTTTATACAGTAAACTTAAAT
GAAATGCCCAAAACAGAAGTAATATGGCAACAGAAACTGACATGGCGATCAAGACAACAG
GATCGAGAAAACTGTGCTATGAAAGGCAAGCATAAAGATGAATGCCACAACTTTATCAAA
GTATTTGTTCCAAGAAACGATGAGATGGTTTTTGTTTGTGGTACCAATGCATTCAATCCC
ATGTGTAGATACTACAGGGTAAGTACCTTAGAATATGATGGGGAAGAAATTAGTGGCCTG
GCAAGATGCCCATTTGATGCCAGACAAACCAATGTTGCCCTCTTTGCTGATGGGAAGCTG
TATTCTGCCACAGTGGCTGACTTCTTGGCCAGCGATGCCGTTATTTATCGAAGCATGGGT
GATGGATCTGCCCTTCGCACAATAAAATATGATTCCAAATGGATAAAAGAGCCACACTTT
CTTCATGCCATAGAATATGGAAACTATGTCTATTTCTTCTTTCGAGAAATCGCTGTCGAA
CATAATAATTTAGGCAAGGCTGTGTATTCCCGCGTGGCCCGCATATGTAAAAACGACATG
GGTGGTTCCCAGCGGGTCCTGGAGAAACACTGGACTTCATTTCTAAAGGCTCGGCTGAAC
TGTTCTGTCCCTGGAGATTCGTTTTTCTACTTTGATGTTCTGCAGTCTATTACAGACATA
ATACAAATCAATGGCATCCCCACTGTGGTCGGGGTGTTTACCACGCAGCTCAATAGCATC
CCTGGTTCTGCTGTCTGTGCATTTAGCATGGATGACATTGAAAAAGTATTCAAAGGACGG
TTTAAGGAACAGAAAACTCCAGATTCTGTTTGGACAGCAGTTCCCGAAGACAAAGTGCCA
AAGCCAAGGCCTGGCTGTTGTGCAAAACACGGCCTTGCCGAAGCTTATAAAACCTCCATC
GATTTCCCGGATGAAACTCTGTCATTCATCAAATCTCATCCCCTGATGGACTCTGCCGTT
CCACCCATTGCCGATGAGCCCTGGTTCACAAAGACTCGGGTCAGGTACAGACTGACGGCC
ATCTCAGTGGACCATTCAGCCGGACCCTACCAGAACTACACAGTCATCTTTGTTGGCTCT
GAAGCTGGCATGGTACTTAAAGTTCTGGCAAAGACCAGTCCTTTCTCTTTGAACGACAGC
GTATTACTGGAAGAGATTGAAGCCTACAACCATGCAAAGTGCAGTGCTGAGAATGAGGAA
GACAAAAAGGTCATCTCATTACAGTTGGATAAAGATCACCACGCTTTATATGTGGCGTTC
TCTAGCTGCATTATCCGCATCCCCCTCAGTCGCTGTGAGCGTTATGGATCATGTAAAAAG
TCTTGTATTGCATCTCGTGACCCGTATTGTGGCTGGTTAAGCCAGGGATCCTGTGGTAGA
GTGACCCCAGGGATGCTGCTGTTAACCGAAGACTTCTTTGCTTTCCATAACCACAGTGCT
GAAGGATATGAACAAGACACAGAATTCGGCAACACAGCTCATCTAGGGGACTGCCATGAA
ATTTTGCCTACTTCAACTACACCAGATTACAAAATATTTGGCGGTCCAACATCTGACATG
GAGGTATCTTCATCTTCTGTTACCACAATGGCAAGTATCCCAGAAATCACACCTAAAGTG
ATTGATACCTGGAGACCTAAACTGACAAGCTCTCGGAAATTTGTAGTTCAAGATGATCCA
AACACTTCTGATTTTACTGATCCTTTATCGGGTATCCCAAAGGGTGTACGATGGGAAGTC
CAGTCTGGAGAGTCCAACCAGATGGTCCACATGAATGTCCTCATCACCTGTGTCTTTGCT
GCTTTTGTTTTGGGGGCATTCATTGCAGGTGTGGCAGTATACTGCTATCGAGACATGTTT
GTTCGGAAAAACAGAAAGATCCATAAAGATGCAGAGTCCGCCCAGTCATGCACAGACTCC
AGTGGAAGTTTTGCCAAACTGAATGGTCTCTTTGACAGCCCTGTCAAGGAATACCAACAG
AATATTGATTCTCCTAAACTGTATAGTAACCTGCTAACCAGTCGGAAAGAGCTACCACCC
AATGGAGATACTAAATCCATGGTAATGGACCATCGAGGGCAACCTCCAGAGTTGGCTGCT
CTTCCTACTCCTGAGTCTACACCCGTGCTTCACCAGAAGACCCTGCAGGCCATGAAGAGC
CACTCAGAAAAGGCCCATGGCCATGGAGCTTCAAGGAAAGAAACCCCTCAGTTTTTTCCG
TCTAGTCCGCCACCTCATTCCCCATTAAGTCATGGGCATATCCCCAGTGCCATTGTTCTT
CCAAATGCTACCCATGACTACAACACGTCTTTCTCAAACTCCAATGCTCACAAAGCTGAA
AAGAAGCTTCAAAACATTGATCACCCTCTCACAAAGTCATCCAGTAAGAGAGATCACCGG
CGTTCTGTTGATTCCAGAAATACCCTCAATGATCTCCTGAAGCATCTGAATGACCCAAAT
AGTAACCCCAAAGCCATCATGGGAGACATCCAGATGGCACACCAGAACTTAATGCTGGAT
CCCATGGGATCGATGTCTGAGGTCCCACCTAAAGTCCCTAACCGGGAGGCATCGCTATAC
TCCCCTCCTTCAACTCTCCCCAGAAATAGCCCAACCAAGCGAGTGGATGTCCCCACCACT
CCTGGAGTCCCAATGACTTCTCTGGAAAGACAAAGAGGTTATCACAAAAATTCCTCCCAG
AGGCACTCTATATCTGCTATGCCTAAAAACTTAAACTCACCAAATGGTGTTTTGTTATCC

AGACAGCCTAGTATGAACCGTGGAGGATATATGCCCACCCCCACTGGGGCGAAGGTGGAC
TATATTCAGGGAACACCAGTGAGTGTTCATCTGCAGCCTTCCCTCTCCAGACAGAGCAGC
TACACCAGTAATGGCACTCTTCCTAGGACGGGACTAAAGAGGACGCCGTCCTTAAAACCT
GACGTGCCACCAAAGCCTTCCTTTGTTCCTCAAACCCCATCTGTCAGACCACTGAACAAA
TACACATAC**TAG**GCCTCAAGTGTGCTATTCCCATGTGGCTTTATCCTGTCCGTGTTGTTG
AGAG

The nucleic acid sequence of NOV4f maps to chromosome 15.

A NOV4f polypeptide (SEQ ID NO:18) encoded by SEQ ID NO:17 is 768 amino acid residues and is presented using the one letter code in Table 4f.

Table 4L. NOV4f protein sequence (SEQ ID NO:20)

MRVFLLCAYILLLMVSQLRAVSFPEDDEPLNTVDYHCKSSRQYPVFRGRPSGNESQHRLD
FQLMLKIRDTLYIAGRDQVYTVNLNEMPKTEVIWQQKLTWRSRQQDRENCAMKGKHKDEC
HNFIKVFVPRNDEMVFVCGTNAFNPMCRYYRVSTLEYDGEEISGLARCPFDARQTNVALF
ADGKLYSATVADFLASDAVIYRSMGDGSALRTIKYDSKWIKEPHFLHAIEYGNYVYFFFR
EIAVEHNNLGKAVYSRVARICKNDMGGSQRVLEKHWTSFLKARLNCSVPGDSFFYFDVLQ
SITDIIQINGIPTVVGVFTTQLNSIPGSAVCAFSMDDIEKVFKGRFKEQKTPDSVWTAVP
EDKVPKPRPGCCAKHGLAEAYKTSIDFPDETLSFIKSHPLMDSAVPPIADEPWFTKTRVR
YRLTAISVDHSAGPYQNYTVIFVGSEAGMVLKVLAKTSPFSLNDSVLLEEIEAYNHAKCS
AENEEDKKVISLQLDKDHHALYVAFSSCIIRIPLSRCERYGSCKKSCIASRDPYCGWLSQ
GSCGRVTPGMLLLTEDFFAFHNHSAEGYEQDTEFGNTAHLGDCHEILPTSTTPDYKIFGG
PTSDMEVSSSSVTTMASIPEITPKVIDTWRPKLTSSRKFVVQDDPNTSDFTDPLSGIPKG
VRWEVQSGESNQMVHMNVLITCVFAAFVLGAFIAGVAVYCYRDMFVRKNRKIHKDAESAQ
SCTDSSGSFAKLNGLFDSPVKEYQQNIDSPKLYSNLLTSRKELPPNGDTKSMVMDHRGQP
PELAALPTPESTPVLHQKTLQAMKSHSEKAHGHGASRKETPQFFPSSPPPHSPLSHGHIP
SAIVLPNATHDYNTSFSNSNAHKAEKKLQNIDHPLTKSSSKRDHRRSVDSRNTLNDLLKH
LNDPNSNPKAIMGDIQMAHQNLMLDPMGSMSEVPPKVPNREASLYSPPSTLPRNSPTKRV
DVPTTPGVPMTSLERQRGYHKNSSQRHSISAMPKNLNSPNGVLLSRQPSMNRGGYMPTPT
GAKVDYIQGTPVSVHLQPSLSRQSSYTSNGTLPRTGLKRTPSLKPDVPPKPSFVPQTPSV
RPLNKYTY

NOV4a also has homology to the amino acid sequences shown in the BLASTP data listed in Table 4M.

Table 4M. BLAST results for NOV4a

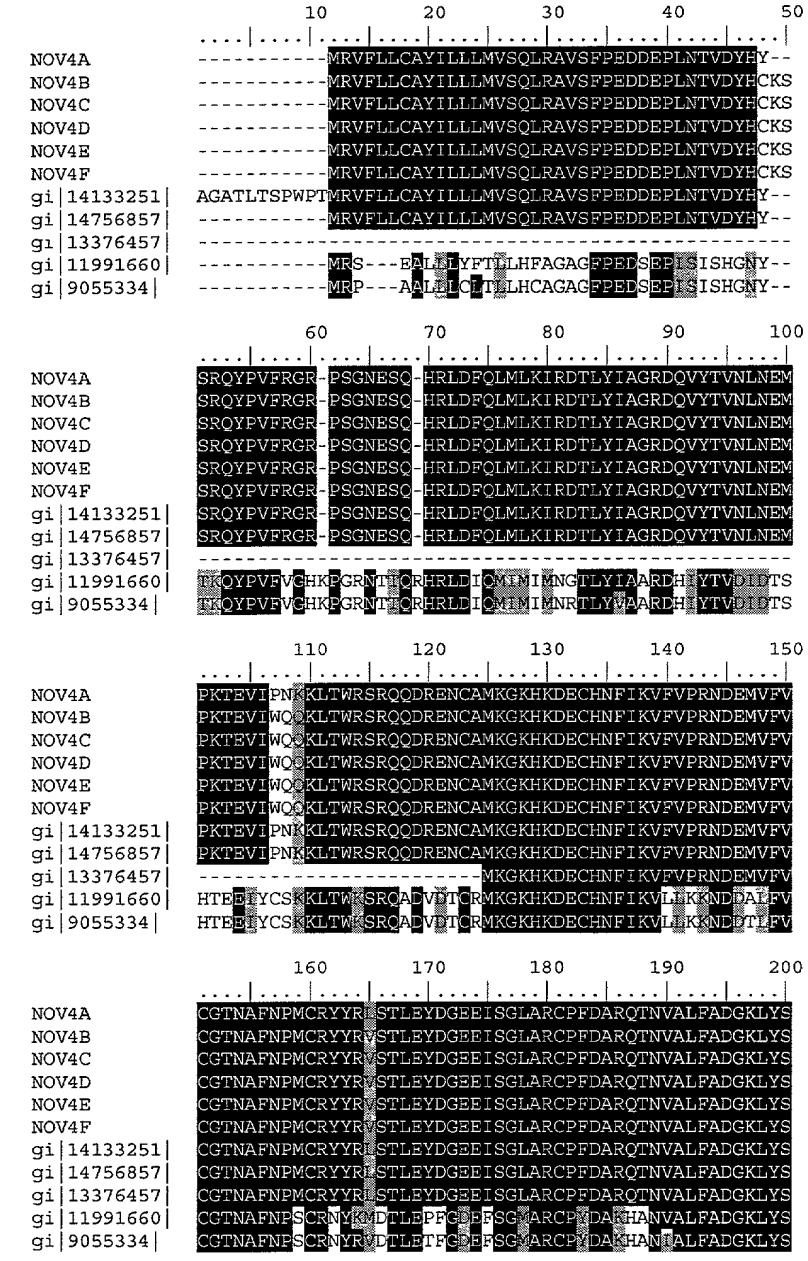
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|14133251|dbj|BAA96003.2| (AB040912)	KIAA1479 protein/human	1022	100	100	0.0
gi|14756857|ref|XP_016482.2 (XM_016482)	hypothetical protein XP_016482 [Homo sapiens]	1011	100	100	0.0
gi|13376457|ref|NP_079242.1 (NM_024966)	hypothetical protein FLJ11598 [Homo sapiens]	367	100	100	0.0
gi|11991660|ref|NP_063847.1 (NM_020796)	Semaphorin 6A1/Human	1030	62	78	e-180

gi|9055334|ref|NP_0 62214.1|	Semaphorin 6A	888	62	78	e-179

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 4N.

Table 4N ClustalW Analysis of NOV4

1) NOV4a (SEQ ID NO:16)
2) NOV4b (SEQ ID NO:18)
3) gi|14133251| (SEQ ID NO: 60)
4) gi|14756857| (SEQ ID NO: 61)
5) gi|13376457|(SEQ ID NO: 62)
6) gi|11991660| (SEQ ID NO: 63)
7) gi|9055334| (SEQ ID NO: 64)



```
                        210       220       230       240       250
               ....|....|....|....|....|....|....|....|....|....|
NOV4A          ATVADFLASDAVIYRSMGDGSALRTIKYDSKWIKEPHFLHAIEYGNYVYF
NOV4B          ATVADFLASDAVIYRSMGDGSALRTIKYDSKWIKEPHFLHAIEYGNYVYF
NOV4C          ATVADFLASDAVIYRSMGDGSALRTIKYDSKWIKEPHFLHAIEYGNYVYF
NOV4D          ATVADFLASDAVIYRSMGDGSALRTIKYDSKWIKEPHFLHAIEYGNYVYF
NOV4E          ATVADFLASDAVIYRSMGDGSALRTIKYDSKWIKEPHFLHAIEYGNYVYF
NOV4F          ATVADFLASDAVIYRSMGDGSALRTIKYDSKWIKEPHFLHAIEYGNYVYF
gi|14133251|   ATVADFLASDAVIYRSMGDGSALRTIKYDSKWIKEPHFLHAIEYGNYVYF
gi|14756857|   ATVADFLASDAVIYRSMGDGSALRTIKYDSKWIKEPHFLHAIEYGNYVYF
gi|13376457|   ATVADFLASDAVIYRSMGDGSALRTIKYDSKWIKEPHFLHAIEYGNYVYF
gi|11991660|   ATVTDFLAIDAVIYRSLGESPTLRTVKHDSKWLKEPYFVQAVDYGDYIYF
gi|9055334|    ATVTDFLAIDAVIYRSLGDSPTLRTVKHDSKWLKEPYFVQAVDYGDYIYF

                        260       270       280       290       300
               ....|....|....|....|....|....|....|....|....|....|
NOV4A          FFREIAVEHNNLGKAVYSRVARICKNDMGGSQRVLEKHWTSFLKARLNCS
NOV4B          FFREIAVEHNNLGKAVYSRVARICKNDMGGSQRVLEKHWTSFLKARLNCS
NOV4C          FFREIAVEHNNLGKAVYSRVARICKNDMGGSQRVLEKHWTSFLKARLNCS
NOV4D          FFREIAVEHNNLGKAVYSRVARICKNDMGGSQRVLEKHWTSFLKARLNCS
NOV4E          FFREIAVEHNNLGKAVYSRVARICKNDMGGSQRVLEKHWTSFLKARLNCS
NOV4F          FFREIAVEHNNLGKAVYSRVARICKNDMGGSQRVLEKHWTSFLKARLNCS
gi|14133251|   FFREIAVEHNNLGKAVYSRVARICKNDMGGSQRVLEKHWTSFLKARLNCS
gi|14756857|   FFREIAVEHNNLGKAVYSRVARICKNDMGGSQRVLEKHWTSFLKARLNCS
gi|13376457|   FFREIAVEHNNLGKAVYSRVARICKNDMGGSQRVLEKHWTSFLKARLNCS
gi|11991660|   FFREIAVEYNTMGKVVFPRVAQVCKNDMGGSQRVLEKQWTSFLKARLNCS
gi|9055334|    FFREIAVEYNTMGKVVFPRVAQVCKNDMGGSQRVLEKQWTSFLKARLNCS

                        310       320       330       340       350
               ....|....|....|....|....|....|....|....|....|....|
NOV4A          VPGDSFFYFDVLQSITDIIQINGIPTVVGVFTTQLNSIPGSAVCAFSMDD
NOV4B          VPGDSFFYFDVLQSITDIIQINGIPTVVGVFTTQLNSIPGSAVCAFSMDD
NOV4C          VPGDSFFYFDVLQSITDIIQINGIPTVVGVFTTQLNSIPGSAVCAFSMDD
NOV4D          VPGDSFFYFDVLQSITDIIQINGIPTVVGVFTTQLNSIPGSAVCAFSMDD
NOV4E          VPGDSFFYFDVLQSITDIIQINGIPTVVGVFTTQLNSIPGSAVCAFSMDD
NOV4F          VPGDSFFYFDVLQSITDIIQINGIPTVVGVFTTQLNSIPGSAVCAFSMDD
gi|14133251|   VPGDSFFYFDVLQSITDIIQINGIPTVVGVFTTQLNSIPGSAVCAFSMDD
gi|14756857|   VPGDSFFYFDVLQSITDIIQINGIPTVVGVFTTQLNSIPGSAVCAFSMDD
gi|13376457|   VPGDSFFYFDVLQSITDIIQINGIPTVVGVFTTQLNSIPGSAVCAFSMDD
gi|11991660|   VPGDSHFYFNILQAVTDVIRINGRDVVLATFSTPYNSIPGSAVCAYDMLD
gi|9055334|    VPGDSHFYFNILQAVTDVIRINGRDVVLATFSTPYNSIPGSAVCAYDMLD

                        360       370       380       390       400
               ....|....|....|....|....|....|....|....|....|....|
NOV4A          IEKVFKGRFKEQKTPDSVWTAVPEDKVPKPRPGCCAKHGLAEAYKTSIDF
NOV4B          IEKVFKGRFKEQKTPDSVWTAVPEDKVPKPRPGCCAKHGLAEAYKTSIDF
NOV4C          IEKVFKGRFKEQKTPDSVWTAVPEDKVPKPRPGCCAKHGLAEAYKTSIDF
NOV4D          IEKVFKGRFKEQKTPDSVWTAVPEDKVPKPRPGCCAKHGLAEAYKTSIDF
NOV4E          IEKVFKGRFKEQKTPDSVWTAVPEDKVPKPRPGCCAKHGLAEAYKTSIDF
NOV4F          IEKVFKGRFKEQKTPDSVWTAVPEDKVPKPRPGCCAKHGLAEAYKTSIDF
gi|14133251|   IEKVFKGRFKEQKTPDSVWTAVPEDKVPKPRPGCCAKHGLAEAYKTSIDF
gi|14756857|   IEKVFKGRFKEQKTPDSVWTAVPEDKVPKPRPGCCAKHGLAEAYKTSIDF
gi|13376457|   IEKVFKGRFKEQKTPDSVWTAVPEDKVPKPRPGCCAKHGLAEAYKTSIDF
gi|11991660|   IASVFTGRFKEQKSPDSTWTPVPDERVPKPRPGCCAGSSSLERYATSNEF
gi|9055334|    IANVFTGRFKEQKSPDSTWTPVPDERVPKPRPGCCAGSSSLEKYATSNEF

                        410       420       430       440       450
               ....|....|....|....|....|....|....|....|....|....|
NOV4A          PDETLSFIKSHPLMDSAVPPIADEPWFTKTRVRYRLTAISVDHSAGPYQN
NOV4B          PDETLSFIKSHPLMDSAVPPIADEPWFTKTRVRYRLTAISVDHSAGPYQN
NOV4C          PDETLSFIKSHPLMDSAVPPIADEPWFTKTRVRYRLTAISVDHSAGPYQN
NOV4D          PDETLSFIKSHPLMDSAVPPIADEPWFTKTRVRYRLTAISVDHSAGPYQN
NOV4E          PDETLSFIKSHPLMDSAVPPIADEPWFTKTRVRYRLTAISVDHSAGPYQN
NOV4F          PDETLSFIKSHPLMDSAVPPIADEPWFTKTRVRYRLTAISVDHSAGPYQN
gi|14133251|   PDETLSFIKSHPLMDSAVPPIADEPWFTKTRVRYRLTAISVDHSAGPYQN
gi|14756857|   PDETLSFIKSHPLMDSAVPPIADEPWFTKTRVRYRLTAISVDHSAGPYQN
gi|13376457|   PDETLSFIKSHPLMDSAVPPIADEPWFTKTRVRYRLTAISVDHSAGPYQN
gi|11991660|   PDDTLNFIKTHPLMDEAVPSIFNRPWFLRTMVRYRLTKIAVDTAAGPYQN
gi|9055334|    PDDTLNFIKTHPLMDEAVPSIINRPWFLRTMVRYRLTKIAVDNAAGPYQN

                        460       470       480       490       500
               ....|....|... |....|....|....|....|....|....|....|
NOV4A          YTVIFVGSEAGMVLKVLAKT-SPFSLNDSVLLEEIEAYNHAK--------
NOV4B          YTVIFVGSEAGMVLKVLAKT-SPFSLNDSVLLEEIEAYNHAKCSAENEED
NOV4C          YTVIFVGSEAGMVLKVLAKT-SPFSLNDSVLLEEIEAYNHAKCSAENEED
NOV4D          YTVIFVGSEAGMVLKVLAKT-SPFSLNDSVLLEEIEAYNHAKCSAENEED
NOV4E          YTVIFVGSEAGMVLKVLAKT-SPFSLNDSVLLEEIEAYNHAKCSAENEED
NOV4F          YTVIFVGSEAGMVLKVLAKT-SPFSLNDSVLLEEIEAYNHAKCSAENEED
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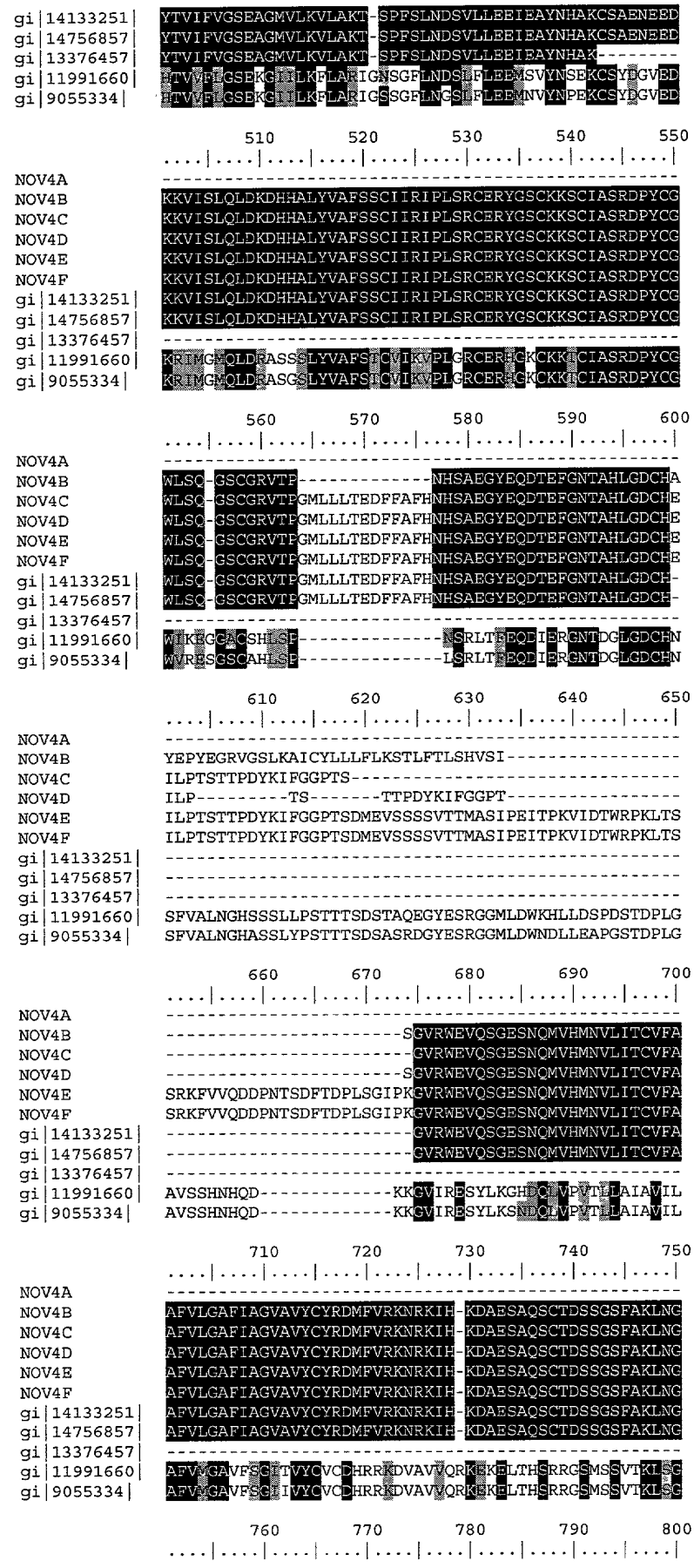

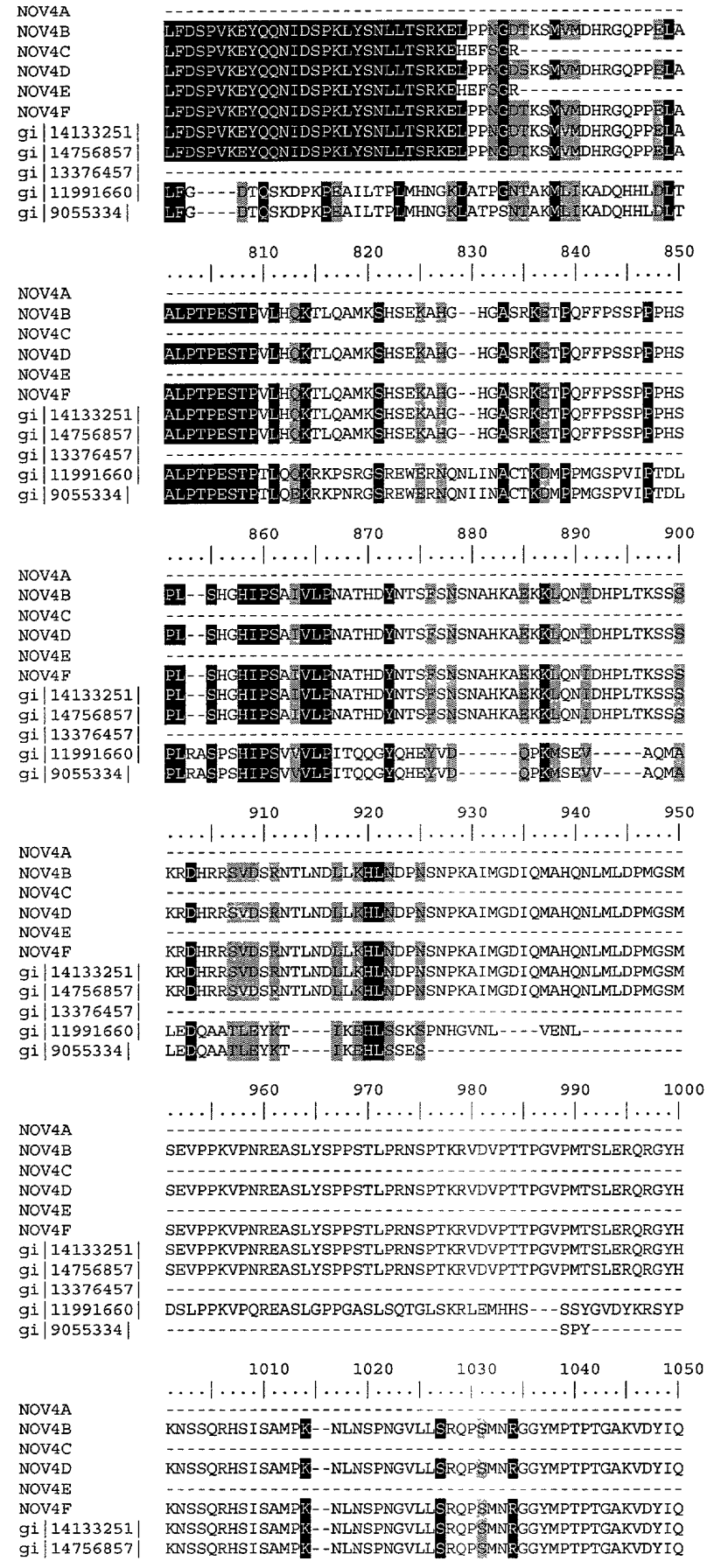
NOV4A
NOV4B
NOV4C
NOV4D
NOV4E
NOV4F
gi|14133251|
gi|14756857|
gi|13376457|
gi|11991660|
gi|9055334|
810 820 830 840 850
860 870 880 890 900
910 920 930 940 950
960 970 980 990 1000
1010 1020 1030 1040 1050

```
gi|13376457|  --------------------------------------------------
gi|11991660|  TNSLTRSHQATTLKRNNTNSSNSSHLSRNQSFGRGD-NPPPAPQRVDSIQ
gi|9055334|   -----------VLK----------QFS--EAFNR----------------

                        1060      1070      1080      1090      1100
                  ....|....|....|....|....|....|....|....|....|....|
NOV4A             --------------------------------------------------
NOV4B             G-TPVSVHLQPSLSRQSSYTSNGTLPRTGLKRTPSLKPDVPPKPSFVPQT
NOV4C             --------------------------------------------------
NOV4D             G-TPVSVHLQPSLSRQSSYTSNGTLPRTGLKRTPSLKPDVPPKPSFVPQT
NOV4E             --------------------------------------------------
NOV4F             G-TPVSVHLQPSLSRQSSYTSNGTLPRTGLKRTPSLKPDVPPKPSFVPQT
gi|14133251|      G-TPVSVHLQPSLSRQSSYTSNGTLPRTGLKRTPSLKPDVPPKPSFVPQT
gi|14756857|      G-TPVSVHLQPSLSRQSSYTSNGTLPRTGLKRTPSLKPDVPPKPSFVPQT
gi|13376457|      --------------------------------------------------
gi|11991660|      VHSSQPSGQAVTVSRQPSLNAYNSLTRSGLKRTPSLKPDVPPKPSFAPLS
gi|9055334|       ------QGIILSVAVE---------------------------------

                        1110
                  ....|....|.
NOV4A             -----------
NOV4B             PSVRPLNKYTY
NOV4C             -----------
NOV4D             PSVRPLNKYTY
NOV4E             -----------
NOV4F             PSVRPLNKYTY
gi|14133251|      PSVRPLNKYTY
gi|14756857|      PSVRPLNKYTY
gi|13376457|      -----------
gi|11991660|      TSMKPNDACT-
gi|9055334|       -----------
```

Tables 4O lists the domain description from DOMAIN analysis results against NOV4a. This indicates that the NOV4a sequence has properties similar to those of other proteins known to contain this domain.

Table 4N. Domain Analysis of NOV4a

gnl Smart|smart00630, Sema, semaphorin domain

CD-Length = 430 residues, 96.0% aligned

Score = 436 bits (1122), Expect = 1e-123

The semaphorin/collapsin family of molecules plays a critical role in the guidance of growth cones during neuronal development. See semaphorin 3F (601124). They represent a family of conserved genes that encode nerve growth cone guidance signals. In the process of constructing a complete cosmid/P1 contig covering this region for the positional cloning of oncogenes, Sekido et al. (1996) identified 2 additional members of the human semaphorin family, semaphorin 3B, which they called semaphorin A(V), and semaphorin 3F, which they called semaphorin IV, in chromosome region 3p21.3. The 2 genes lie within approximately 70 kb of each other, to have widespread but distinct patterns of expression in nonneural tissues, and to have different patterns of expression in lung cancer. Human semaphorin A(V) has 86% amino acid homology with murine semaphorin A, whereas semaphorin IV is more closely

related to murine semaphorin E, with 50% homology. The 2 semaphorin genes are flanked by 2 GTP-binding protein genes, GNAI2 (139360) and GNAT1 (139330). Sekido et al. (1996) stated that other human semaphorin gene sequences, for example, human semaphorin III (SEMA3A; 603961) and homologs of murine semaphorins B (SEMA4A) and C (SEMA4B), are not located on chromosome 3. Sekido et al. (1996) showed that human semaphorin A(V) is translated in vitro into a 90-kD protein that accumulates in the endoplasmic reticulum. Human semaphorin A(V) was expressed in only 1 out of 23 small cell lung cancers (SCLCs) and 7 out of 16 non-SCLCs, whereas semaphorin IV was expressed in 19 out of 23 SCLCs and 13 out of 16 non-SCLCs. Mutational analysis of semaphorin A(V) revealed mutations (germline in 1 case) in 3 of 40 lung cancers.

The semaphorins are a family of proteins that are involved in signaling. All the family members have a secretion signal, a 500-amino acid sema domain, and 16 conserved cysteine residues (Kolodkin et al., 1993). Sequence comparisons have grouped the secreted semaphorins into 3 general classes, all of which also have an immunoglobulin domain. The semaphorin III family, consisting of human semaphorin III (SEMA3A; 603961), chicken collapsin, and mouse semaphorins A, D, and E, all have a basic domain at the C terminus. Chicken collapsin contributes to path finding by axons during development by inhibiting extension of growth cones Luo et al. (1993) through an interaction with a collapsin response mediator protein of relative molecular mass 62K (CRMP-62) (Goshima et al., 1995), a putative homolog of an axonal guidance associated UNC-33 gene product (601168). Xiang et al. (1996) isolated a novel human semaphorin, which they termed semaphorin III/F, from a region of the 3p21.3 region involved in homozygous deletions in 2 small cell lung cancer (SCLC) cell lines. The gene was expressed as a 3.8-kb transcript in a variety of cell lines and tissues. It was detected as early as embryonic day 10 in mouse development. There was high expression in mammary gland, kidney, fetal brain, and lung and lower expression in heart and liver. Although there was reduced expression of the gene in several SCLC lines, no mutations were found. The new gene had characteristics of a secreted member of the semaphorin III family, with 52% identity with mouse semaphorin E and 49% identity with chicken collapsin/semaphorin D. Sekido et al. (1996) localized the SEMA3F and SEMA3B (601281) genes to 3p21.3.

The semaphorins comprise a large family of membrane-bound and secreted proteins, some of which have been shown to function in axon guidance. See semaphorin 3F (601124). Encinas et al. (1999) cloned a novel semaphorin, which they referred to as semaphorin W (SEMAW). Sequence analysis of the SEMAW gene indicated that SEMAW

is a member of the class IV subgroup of transmembrane semaphorins. The mouse and rat forms of semaphorin W share 97% amino acid sequence identity, and each shows approximately 91% identity with the human form. The SEMAW gene contains 15 exons, up to 4 of which were absent in the human cDNAs sequenced by Encinas et al. (1999). Expression studies showed that SEMAW mRNA is expressed at high levels in postnatal brain and lung and, unlike many other semaphorins, at low levels in the developing embryo. Functional studies showed that semaphorin W can collapse retinal ganglion cell axons. By genetic mapping with human/hamster radiation hybrids, Encinas et al. (1999) mapped the human SEMAW gene to chromosome 2p13. By genetic mapping with mouse/hamster radiation hybrids, they mapped the mouse Semaw gene to chromosome 6; physical mapping placed the gene on BACs carrying microsatellite markers D6Mit70 and D6Mit189. This localization placed the mouse Semaw gene within the locus for motor neuron degeneration-2 of mouse, making it an attractive candidate for that disorder.

Neural networks that are very complicated but specific to each neuron are formed during development when growth cones make specific pathway choices and find their correct targets using a variety of guidance molecules in their surroundings. The semaphorins (SEMAs) are a family of transmembrane and secreted proteins that appear to function during growth cone guidance. These proteins contain a conserved sema domain of approximately 500 amino acids. Inagaki et al. (1995) cloned a novel mouse semaphorin gene, which they named semaphorin F (SemaF). In situ hybridization detected SemaF expression throughout the brain and spinal cord of E15.5, E16.5, and P1 mice. In the central nervous system, expression was very high in the primordia of the neocortex, hippocampus, thalamus, hypothalamus, tectum, pontine nuclei, spinal cord, and retina. High expression was also found in the primordia of various tissues, such as the olfactory epithelium, epithelium of the vomeronasal organ, enamel epithelium of teeth, anterior and intermediate lobes of the pituitary, epithelium of the inner ear, and sensory ganglia, including trigeminal and dorsal root ganglia. In addition, SemaF was expressed in the lung and kidney. In adult mice, SemaF expression was markedly decreased, with very low expression in several restricted regions of the brain, including the hippocampus. Inagaki et al. (1995) suggested that SemaF functions in forming the neural network during development.

The semaphorins are a family of proteins thought to be involved in axonal guidance. Most of the known semaphorins have a similar primary structure characterized by the semaphorin domain and a carboxy-terminal Ig motif. Here we report the cloning of two members (semF and G) of a novel class of membrane-bound semaphorins which contain

seven carboxy-terminal thrombospondin repeats, a motif known to promote neurite outgrowth. SemF and G transcripts are expressed, together with semD and E, in specific regions of young mouse embryos, demarcating distinct compartments of the developing somites or the undifferentiated neuroepithelium. The identification of semF and G increases the number of vertebrate semaphorins to at least 20 and suggests that some semaphorins might act as positive axonal guidance cues.

The disclosed NOV4 nucleic acid of the invention encoding a Semaphorin-like protein includes the nucleic acid whose sequence is provided in Table 4A, or 4C or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 4A or 4C while still encoding a protein that maintains its Semaphorin-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 0 percent of the bases may be so changed.

The disclosed NOV4 protein of the invention includes the Semaphorin-like protein whose sequence is provided in Table 4B or 4D. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 4B or 4D while still encoding a protein that maintains its Semaphorin-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 0 percent of the residues may be so changed.

The protein similarity information, expression pattern, and map location for the semaphorin-like protein and nucleic acid (NOV4) disclosed herein suggest that this NOV4 protein may have important structural and/or physiological functions characteristic of the Semaphorin family. Therefore, the NOV4 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications. These include serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic

applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo.

The NOV4 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from Parkinson's disease , psychotic and neurological disorders, Alzheimers disease, Lung and other cancers and/or other pathologies. The NOV4 nucleic acids, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV4 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example, the disclosed NOV4a protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV4 epitope is from about amino acids 1 to 10. In another embodiment, a NOV4 epitope is from about amino acids 170 to 200. In additional embodiments, NOV4 epitopes are from about amino acids 270 to 325, and from about amino acids 425 to 460. These novel proteins can be used in assay systems for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV5

NOV5 includes two novel serine/threonine kinase-like proteins disclosed below. The disclosed sequences have been named NOV5a and NOV5b.

NOV5a

A disclosed NOV5a nucleic acid of 2388 nucleotides (also referred to as CG50211-01) encoding a novel serine/threonine kinase-like protein is shown in Table 5A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 201-203 and ending with a TGA codon at nucleotides 2295-2297.

Table 5A. NOV5a Nucleotide Sequence (SEQ ID NO:21)

TGCACGGGGCCACTAGGACCCTCGGCGTCCCTTCCCCTCCCCCGCCCTGCCCCCTCTCCCGCCGCGCGGA
CCCGGGCGTTCTCGGCGCCCAGCTTTTGAGCTCGCGTCCCCAGGCCGGCGGGGGGGGAGGGGAAGAGAGG
GGACCCTGGGACCCCCGCCCCCCCCACCCGGCCGCCCCTGCCCCCCGGGACCCGGAGAAGATGTCTTCGC
GGACGGTGCTGGCCCCGGGCAACGATCGGAACTCGGACACGCATGGCACCTTGGGCAGTGGCCGCTCCTC
GGACAAAGGCCCGTCCTGGTCCAGCCGCTCACTGGGTGCCCGTTGCCGGAACTCCATCGCCTCCTGTCCC
GAGGAGCAGCCCCACGTGGGCAACTACCGCCTGCTGAGGACCATTGGGAAGGGCAACTTTGCCAAAGTCA
AGCTGGCTCGGCACATCCTCACTGGTCGGGAGGTTGCCATCAAGATTATCGACAAAACCCAGCTGAATCC
CAGCAGCCTGCAGAAGCTGTTCCGAGAAGTCCGCATCATGAAGGGCCTAAACCACCCCAACATCGTGAAG
CTCTTTGAGGTGATTGAGACTGAGAAGACGCTGTACCTGGTGATGGAGTACGCAAGTGCTGGTGAGCCGC
CCACCCTCTCCGCCCTGCCCCTGTGCCACCTCCCCCTGCCGCTGCACCTGACCCTGACCCCGCTCGGCCT
CTGCCCTGCAGGAGAAGTGTTTGACTACCTCGTGTCGCATGGCCGCATGAAGGAGAAGGAAGCTCGAGCC
AAGTTCCGACAGATTGTTTCGGCTGTGCACTATTGTCACCAGAAAAATATTGTACACAGGGACCTGAAGG
CTGAGAACCTCTTGCTGGATGCCGAGGCCAACATCAAGATTGCTGACTTTGGCTTCAGCAACGAGTTCAC
ACTGGGATCGAAGCTGGACACGTTCTGCGGGAGCCCCCCATATGCCGCCCCGGAGCTGTTTCAGGGCAAG
AAGTACGACGGGCCGGAGGTGGACATCTGGAGCCTGGGAGTCATCCTGTACACCCTCGTCAGCGGCTCCC
TGCCCTTCGACGGGCACAACCTCAAGGAGCTGCGGGAGCGAGTACTCAGAGGGAAGTACCGGGTCCCTTT
CTACATGTCAACAGACTGTGAGAGCATCCTGCGGAGATTTTTGGTGCTGAACCCAGCTAAACGCTGTACT
CTCGAGCAAATCATGAAAGACAAATGGATCAACATCGGCTATGAGGGTGAGGAGTTGAAGCCATACACAG
AGCCCGAGGAGGACTTCGGGGACACCAAGAGAATTGAGGTGATGGTGGGTATGGGCTACACACGGGAAGA
AATCAAAGAGTCCTTGACCAGCCAGAAGTACAACGAAGTGACCGCCACCTACCTCCTGCTGGGCAGGAAG
CTGAGCCCGACGAGCACGGGGGAGGCGGAGCTGAAGGAGGAGCGGCTGCCAGGCCGGAAGGCGAGCTGCA
GCACCGCGGGGAGTGGGAGTCGAGGGCTGCCCCCCTCCAGCCCCATGGTCAGCAGCGCCCACAACCCCAA
CAAGGCAGAGATCCCAGAGCGGCGGAAGGACAGCACGCCGGTGAGTGACCAGGGCTGGGGGATGATGACC
CGCAGAAACACCTACGTTTGCACAGAACGCCCGGGGGCTGAGCGCCCGTCACTGTTGCCAAATGGGAAAG
AAAACCGGGTGCCCCCTGCCTCCCCCTCCAGTCACAGCCTGGCACCCCCATCAGGGGAGCGGAGCCGCCT
GGCACGTGGTTCCACCATCCGCAGCACCTTCCATGGTGGCCAGGTCCGGGACCGGCGGGCAGGGGGTGGG
GGTGGTGGGGGTGTGCAGAATGGGCCCCCTGCCTCTCCCACACTGGCCCATGAGGCTGCACCCCTGCCCG
CCGGGCGGCCCCGCCCCACCACCAACCTCTTCACCAAGCTGACCTCCAAACTGACCCGATCTCGCCTCAG
TTGCCATCTACCTTGGGATCAAACGGAAACCGCCCCCCGGCTGCTCCGATTCCCCTGGAGTGTGAAGCTG
ACCAGCTCGCGCCCTCCTGAGGCCCTGATGGCAGCTCTGCGCCAGGCCACAGCAGCCGCCCGCTGCCGCT
GCCGCCAGCCACAGCCGTTCCTGCTGGCCTGCCTGCACGGGGGTGCGGGCGGGCCCGAGCCCCTGTCCCA
CTTCGAAGTGGAGGTCTGCCAGCTGCCCCGGCCAGGCTTGCGGGGAGTTCTCTTCCGCCGTGTGGCGGGC
ACCGCCCTGGCCTTCCGCACCCTCGTCACCCGCATCTCCAACGACCTCGAGCTCTGAGCCACCACGGTCC
CAGGGCCCTTACTCTTCCTCTCCCTTGTCGCCTTCACTTCTACAGGAGGGGAAGGGGCCAGGGAGGGGAT
TCTCCCTT

The NOV5a nucleic acid was identified on chromosome 19 and has 592 of 842 bases (70%) identical to a gb:GENBANK-ID:RNMARK1|acc:Z83868.1 mRNA from Rattus norvegicus (R.norvegicus mRNA for serine/threonine kinase MARK1).

A disclosed NOV5a polypeptide (SEQ ID NO:20) encoded by SEQ ID NO:19 is 698 amino acid residues and is presented using the one-letter code in Table 5B. Signal P, Psort and/or Hydropathy results predict that NOV5a has no signal peptide and is likely to be localized in the cytoplasm with a certainty of 0.4500. In other embodiments, NOV5a may also be localized to the microbody with a certainty of 0.300, the mitochondrial matrix space with a certainty of 0.1000, or the lysosome (lumen) with a certainty of 0.1000.

Table 5B. Encoded NOV5a protein sequence (SEQ ID NO:22)

MSSRTVLAPGNDRNSDTHGTLGSGRSSDKGPSWSSRSLGARCRNSIASCPEEQPHVGNYRLLRTIGKGNF
AKVKLARHILTGREVAIKIIDKTQLNPSSLQKLFREVRIMKGLNHPNIVKLFEVIETEKTLYLVMEYASA
GEPPTLSALPLCHLPLPLHLTLTPLGLCPAGEVFDYLVSHGRMKEKEARAKFRQIVSAVHYCHQKNIVHR
DLKAENLLLDAEANIKIADFGFSNEFTLGSKLDTFCGSPPYAAPELFQGKKYDGPEVDIWSLGVILYTLV
SGSLPFDGHNLKELRERVLRGKYRVPFYMSTDCESILRRFLVLNPAKRCTLEQIMKDKWINIGYEGEELK
PYTEPEEDFGDTKRIEVMVGMGYTREEIKESLTSQKYNEVTATYLLLGRKLSPTSTGEAELKEERLPGRK
ASCSTAGSGSRGLPPSSPMVSSAHNPNKAEIPERRKDSTPVSDQGWGMMTRRNTYVCTERPGAERPSLLP
NGKENRVPPASPSSHSLAPPSGERSRLARGSTIRSTFHGGQVRDRRAGGGGGGVQNGPPASPTLAHEAA

PLPAGRPRPTTNLFTKLTSKLTRSRLSCHLPWDQTETAPRLLRFPWSVKLTSSRPPEALMAALRQATAAA
RCRCRQPQPFLLACLHGGAGGPEPLSHFEVEVCQLPRPGLRGVLFRRVAGTALAFRTLVTRISNDLEL

The disclosed NOV5a amino acid sequence have 237 of 401 amino acid residues (59%) identical to, and 279 of 401 amino acid residues (69%) similar to, the 729 amino acid residue ptnr:SPTREMBL-ACC:Q9JKE4 protein from Mus musculus (Mouse) (ELKL MOTIF KINASE 2 SHORT FORM).

NOV5a is expressed in at least : lung, placenta, ovary, liver, lymph, colon, testis, B-cell, muscle, skin, brain, tonsil. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

NOV5b

A disclosed NOV5b nucleic acid of 1549 nucleotides (also referred to as CG50211-02) encoding a novel serine/threonine kinase-like protein is shown in Table 5A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 23-25 and ending with a TGA at nucleotides 1547-1549.

Table 5C. NOV5b Nucleotide Sequence (SEQ ID NO:23)

TGCCCCCCGGGACCCGGAGAAG**ATG**TCTTCGCGGACGGTGCTGGCCCCGGGCAACGATCG
GAACTCGGACACGCATGGCACCTTGGGCAGTGGCCGCTCCTCGGACAAAGGCCCGTCCTG
GTCCAGCCGCTCACTGGGTGCCCGTTGCCGGAACTCCATCGCCTCCTGTCCCGAGGAGCA
GCCCCACGTGGGCAACTACCGCCTGCTGAGGACCATTGGGAAGGGCAACTTTGCCAAAGT
CAAGCTGGCTCGGCACATCCTCACTGGTCGGGAGGTTGCCATCAAGATTATCGACAAAAC
CCAGCTGAATCCCAGCAGCCTGCAGAAGCTGTTCCGAGAAGTCCGCATCATGAAGGGCCT
AAACCACCCCAACATCGTGAAGCTCTTTGAGGTGATTGAGACTGAGAAGACGCTGTACCT
GGTGATGGAGTACGCAAGTGCTGGAGAAGTGTTTGACTACCTCGTGTCGCATGGCCGCAT
GAAGGAGAAGGAAGCTCGAGCCAAGTTCCGACAGATTGTTTCGGCTGTGCACTATTGTCA
CCAGAAAAATATTGTACACAGGGACCTGAAGGCTGAGAACCTCTTGCTGGATGCCGAGGC
CAACATCAAGATTGCTGACTTTGGCTTCAGCAACGAGTTCACGCTGGGATCGAAGCTGGA
CACGTTCTGCGGGAGCCCCCCATATGCCGCCCCGGAGCTGTTTCAGGGCAAGAAGTACGA
CGGGCCGGAGGTGGACATCTGGAGCCTGGGAGTCATCCTGTACACCCTCGTCAGCGGCTC
CCTGCCCTTCGACGGGCACAACCTCAAGGAGCTGCGGGAGCGAGTACTCAGAGGGAAGTA
CCGGGTCCCTTTCTACATGTCAACAGACTGTGAGAGCATCCTGCGGAGATTTTTGGTGCT
GAACCCAGCTAAACGCTGTACTCTCGAGCAAATCATGAAAGACAAATGGATCAACATCGG
CTATGAGGGTGAGGAGTTGAAGCCATACACAGAGCCCGAGGAGGACTTCGGGGACACCAA
GAGAATTGAGGTGATGGTGGGTATGGGCTACACACGGGAAGAAATCAAAGAGTCCTTGAC
CAGCCAGAAGTACAACGAAGTGACCGCCGGGCGGCCCCGCCCCACCACCAACCTCTTCAC
CAAGCTGACCTCCAAACTGACCCGAAGGGTCGCAGACGAACCTGAGAGAATCGGGGGACC
TGAGGTCACAAGTTGCCATCTACCTTGGGATCAAACGGAAACCGCCCCCCGGCTGCTCCG
ATTCCCCTGGAGTGTGAAGCTGACCAGCTCGCGCCCTCCTGAGGCCCTGATGGCAGCTCT
GCGCCAGGCCACAGCAGCCGCCCGCTGCCGCTGCCGCCAGCCACAGCCGTTCCTGCTGGC
CTGCCTGCACGGGGGTGCGGGCGGGCCCGAGCCCCTGTCCCACTTCGAAGTGGAGGTCTG
CCAGCTGCCCCGGCCAGGCTTGCGGGGAGTTCTCTTCCGCCGTGTGGCGGGCACCGCCCT
GGCCTTCCGCACCCTCGTCACCCGCATCTCCAACGACCTCGAGCTC**TGA**

The NOV5b nucleic acid was identified on chromosome 19 and has 1107 of 1108 bases (99%) identical to a gb:GENBANK-ID:AB049127|acc:AB049127.1 mRNA from Homo

sapiens (Homo sapiens MARKL1 mRNA for MAP/microtubule affinity-regulating kinase like 1, complete cds).

A disclosed NOV5b polypeptide (SEQ ID NO:20) encoded by SEQ ID NO:19 is 508 amino acid residues and is presented using the one-letter code in Table 5B. Signal P, Psort and/or Hydropathy results predict that NOV5b has no signal peptide and is likely to be localized in the cytoplasm with a certainty of 0.4500. In other embodiments, NOV5b may also be localized to the microbody with a certainty of 0.300, the mitochondrial matrix space with a certainty of 0.1000, or the lysosome (lumen) with a certainty of 0.1000.

Table 5D. Encoded NOV5b protein sequence (SEQ ID NO:24)

```
MSSRTVLAPGNDRNSDTHGTLGSGRSSDKGPSWSSRSLGARCRNSIASCPEEQPHVGNYR
LLRTIGKGNFAKVKLARHILTGREVAIKIIDKTQLNPSSLQKLFREVRIMKGLNHPNIVK
LFEVIETEKTLYLVMEYASAGEVFDYLVSHGRMKEKEARAKFRQIVSAVHYCHQKNIVHR
DLKAENLLLDAEANIKIADFGFSNEFTLGSKLDTFCGSPPYAAPELFQGKKYDGPEVDIW
SLGVILYTLVSGSLPFDGHNLKELRERVLRGKYRVPFYMSTDCESILRRFLVLNPAKRCT
LEQIMKDKWINIGYEGEELKPYTEPEEDFGDTKRIEVMVGMGYTREEIKESLTSQKYNEV
TAGRPRPTTNLFTKLTSKLTRRVADEPERIGGPEVTSCHLPWDQTETAPRLLRFPWSVKL
TSSRPPEALMAALRQATAAARCRCRQPQPFLLACLHGGAGGPEPLSHFEVEVCQLPRPGL
RGVLFRRVAGTALAFRTLVTRISNDLEL
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The disclosed NOV5b amino acid sequence has 361 of 362 amino acid residues (99%) identical to, and 361 of 362 amino acid residues (99%) similar to, the 688 amino acid residue ptnr:SPTREMBL-ACC:Q9BYD8 protein from Homo sapiens (Human) (MAP/ MICROTUBULE AFFINITY-REGULATING KINASE LIKE 1).

NOV5b is expressed in at least : lung, placenta, ovary, liver, lymph, colon, testis, B-cell, muscle, skin, brain, tonsil. Expression information was derived from the tissue sources of the sequences that were included in the derivation of the sequence of CuraGen Acc. No. CG50211-02.

NOV5a also has homology to the amino acid sequences shown in the BLASTP data listed in Table 5E.

Table 5E. BLAST results for NOV5a

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|14763165 ref|XP_030962.1 (XM_030962)	MAP/microtubule affinity-regulating kinase like 1 [Homo sapiens]	688	77	83	0.0

gi|14017937.db; BAB 47489.1| (AB058763)	KIAA1860 protein [Homo sapiens]	689	77	78	0.0
gi|13899225;ref;NP 113605.1 (NM_031417)	MAP/microtubule affinity-regulating kinase like 1 [Homo sapiens]	688	76	77	0.0
gi|4505103 ref|NP C 02367.1| (NM_002376)	MAP/microtubule affinity-regulating kinase 3 [Homo sapiens]	713	59	70	C.0

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 5F.

Table 5F. Clustal W Sequence Alignment

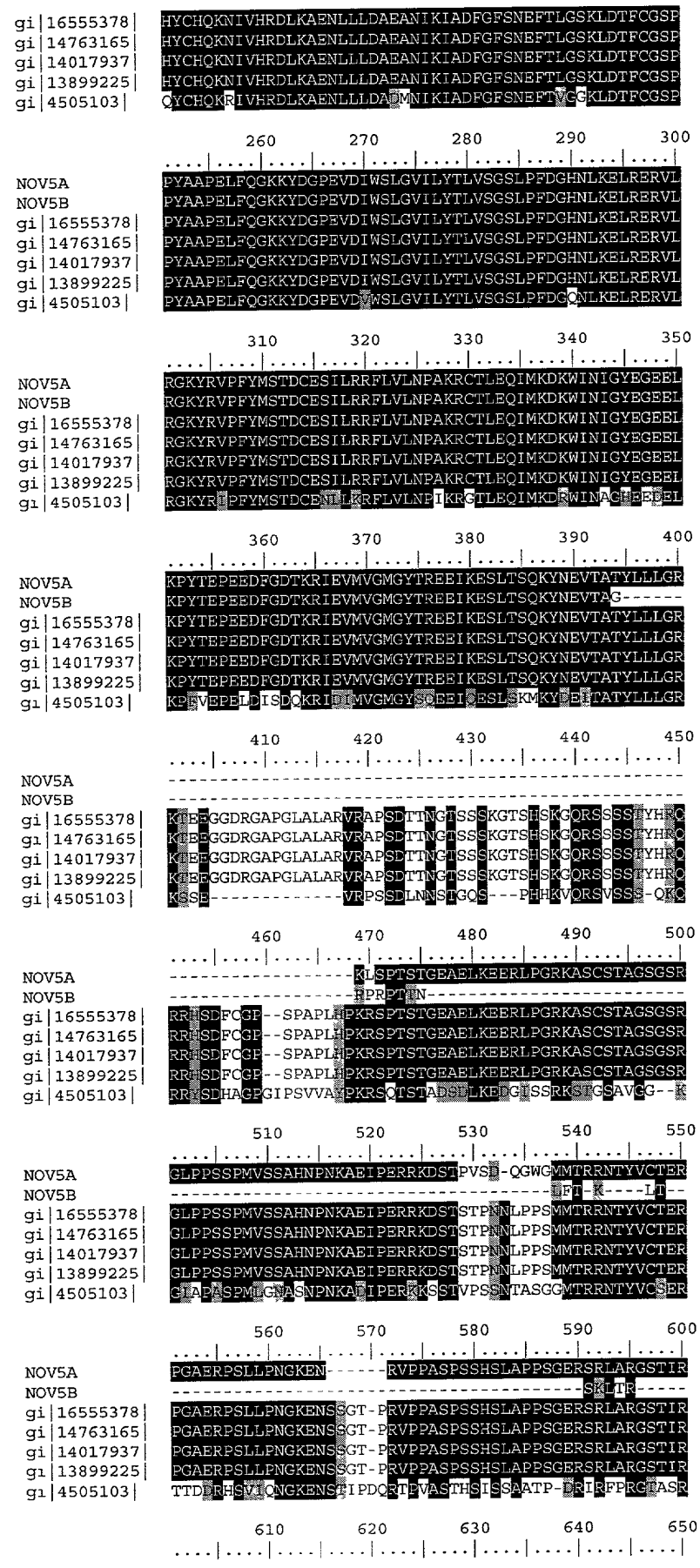
1) NOV5a (SEQ ID NO:20)
2) NOV5b (SEQ ID NO: 22)
3) Gi|16555378| (SEQ ID NO: 70)
4) gi|14763165| (SEQ ID NO: 71)
5) gi|14017937| (SEQ ID NO: 72)
6) gi|13899225| (SEQ ID NO: 73)
7) gi|4505103| (SEQ ID NO: 74)

```
                    60        70        80        90        100
                    ....|....|....|....|....|....|....|....|....|....|
NOV5A               PEEQPHVGNYRLLRTIGKGNFAKVKLARHILTGREVAIKIIDKTQLNPSS
NOV5B               PEEQPHVGNYRLLRTIGKGNFAKVKLARHILTGREVAIKIIDKTQLNPSS
gi|16555378|        PEEQPHVGNYRLLRTIGKGNFAKVKLARHILTGREVAIKIIDKTQLNPSS
gi|14763165|        PEEQPHVGNYRLLRTIGKGNFAKVKLARHILTGREVAIKIIDKTQLNPSS
gi|14017937|        PEEQPHVGNYRLLRTIGKGNFAKVKLARHILTGREVAIKIIDKTQLNPSS
gi|13899225|        PEEQPHVGNYRLLRTIGKGNSAKVKLARHILTGREVAIKIIDKTQLNPSS
gi|4505103|         AEEQPHIGNYRLLRTIGKGNFAKVKLARHILTGREVAIKIIDKTQLNPIS

                    110       120       130       140       150
                    ....|....|....|....|....|....|....|....|....|....|
NOV5A               LQKLFREVRIMKGLNHPNIVKLFEVIETEKTLYLVMEYASAGEPPTLSAL
NOV5B               LQKLFREVRIMKGLNHPNIVKLFEVIETEKTLYLVMEYASAG--------
gi|16555378|        LQKLFREVRIMKGLNHPNIVKLFEVIETEKTLYLVMEYASAG--------
gi|14763165|        LQKLFREVRIMKGLNHPNIVKLFEVIETEKTLYLVMEYASAG--------
gi|14017937|        LQKLFREVRIMKGLNHPNIVKLFEVIETEKTLYLVMEYASAG--------
gi|13899225|        LQKLFREVRIMKGLNHPNIVKLFEVIETEKTLYLVMEYASAG--------
gi|4505103|         LQKLFREVRIMKILNHPNIVKLFEVIEIQKTLYLIMEYASGG--------

                    160       170       180       190       200
                    ....|....|....|....|....|....|....|....|....|....|
NOV5A               PLCHLPLPLHLTLTPLGLCPAGEVFDYLVSHGRMKEKEARAKFRQIVSAV
NOV5B               ----------------------EVFDYLVSHGRMKEKEARAKFRQIVSAV
gi|16555378|        ----------------------EVFDYLVSHGRMKEKEARAKFRQIVSAV
gi|14763165|        ----------------------EVFDYLVSHGRMKEKEARAKFRQIVSAV
gi|14017937|        ----------------------EVFDYLVSHGRMKEKEARAKFRQIVSAV
gi|13899225|        ----------------------EVFDYLVSHGRMKEKEARAKFRQIVSAV
gi|4505103|         ----------------------EVFDYLVSHGRMKEKEARSKFRQIVSAV

                    210       220       230       240       250
                    ....|....|....|....|....|....|....|....|....|....|
NOV5A               HYCHQKNIVHRDLKAENLLLDAEANIKIADFGFSNEFTLGSKLDTFCGSP
NOV5B               HYCHQKNIVHRDLKAENLLLDAEANIKIADFGFSNEFTLGSKLDTFCGSP
```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gi|14763165|
gi|14017937|
gi|13899225|
gi|4505103|
NOV5A
NOV5B
260 270 280 290 300
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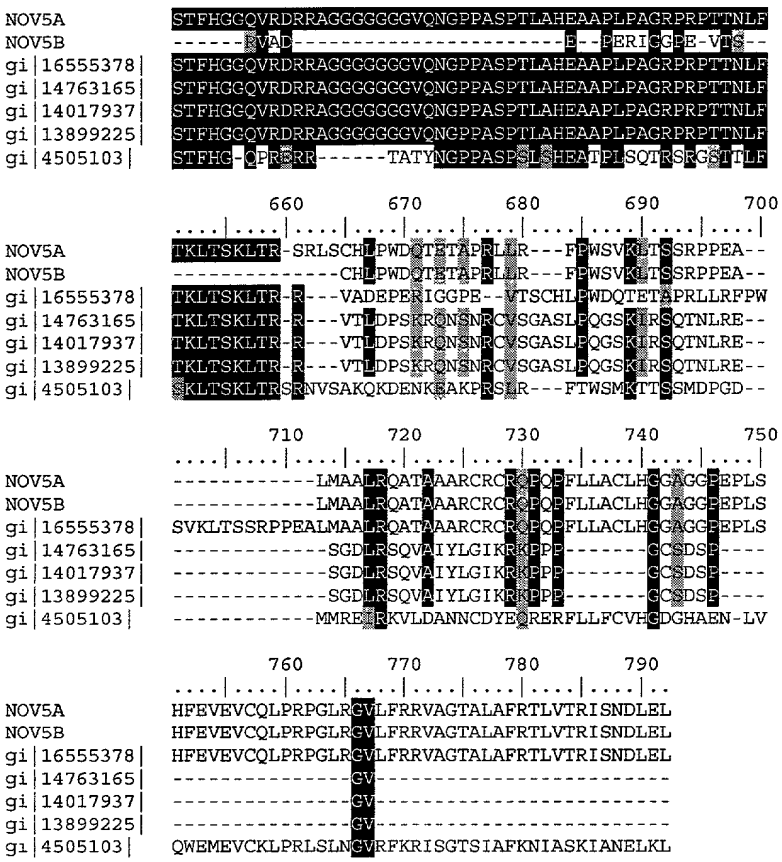
360 370 380 390 400
410 420 430 440 450
460 470 480 490 500
510 520 530 540 550
560 570 580 590 600
610 620 630 640 650



Tables 5G-I list the domain description from DOMAIN analysis results against NOV5a. This indicates that the NOV5a sequence has properties similar to those of other proteins known to contain this domain.

Table 5G. Domain Analysis of NOV5a

gnl|Smart|smart00220, S_TKc, Serine/Threonine protein kinases, catalytic domain; Phosphotransferases. Serine or threonine-specific kinase subfamily

CD-Length = 256 residues, 100.0% aligned

Score = 299 bits (765), Expect = 4e-82

Table 5H. Domain Analysis of NOV5a

gnl|Smart|smart00220, S_TKc, Serine/Threonine protein kinases, catalytic domain; Phosphotransferases. Serine or threonine-specific kinase subfamily

CD-Length = 256 residues, 100.0% aligned

Score = 299 bits (765), Expect = 4e-82

Table 5I. Domain Analysis of NOV5a

gnl|Smart|smart00219, TyrKc, Tyrosine kinase, catalytic domain; Phosphotransferases. Tyrosine-specific kinase subfamily

CD-Length = 258 residues, 98.8% aligned

Score = 150 bits (378), Expect = 3e-37

Eukaryotic protein kinases (Hunter T. (1991) Protein kinase classification. Meth. Enzymol. 200: 3-37) are enzymes that belong to a very extensive family of proteins which share a conserved catalytic core common with both serine/threonine and tyrosine protein kinases. Protein phosphorylation is a fundamental process for the regulation of cellular functions. The coordinated action of both protein kinases and phosphatases controls the levels of phosphorylation and, hence, the activity of specific target proteins. One of the predominant roles of protein phosphorylation is in signal transduction, where extracellular signals are amplified and propagated by a cascade of protein phosphorylation and dephosphorylation events. Two of the best characterized signal transduction pathways involve the cAMP-dependent protein kinase and protein kinase C (PKC). Each pathway uses a different second-messenger molecule to activate the protein kinase, which, in turn, phosphorylates specific target molecules. Extensive comparisons of kinase sequences defined a common catalytic domain, ranging from 250 to 300 amino acids. This domain contains key amino acids conserved between kinases and are thought to play an essential role in catalysis. In the N-terminal extremity of the catalytic domain there is a glycine-rich stretch of residues in the vicinity of a lysine residue, which has been shown to be involved in ATP binding. In the central part of the catalytic domain there is a conserved aspartic acid residue which is important for the catalytic activity of the enzyme (Taylor S.S., Xuong N.-H., Knighton D.R., Zheng J., Ten Eyck L.F., Ashford V.A., Sowadski J.M. (1991) Crystal structure of the

catalytic subunit of cyclic adenosine monophosphate-dependent protein kinase. Science 253: 407-414).

Protein kinases and phosphatases regulate cell-cycle progression, transcription, translation, protein sorting and cell adhesion events that are critical to the inflammatory process. Two of the best-characterized immunosuppressants, cyclosporin and rapamycin, are also effective anti-inflammatory drugs. They act directly on protein phosphorylation and, as such, validate the concept that small-molecule modulators of phosphorylation cascades possess anti-inflammatory properties (Bhagwat SS, Manning AM, Hoekstra MF, Lewis A. Gene-regulating protein kinases as important anti-inflammatory targets. Drug Discov Today. 1999 Oct;4(10):472-479).

Some examples of the role of serine/threonine protein kinases that are important in cell proliferation and disease include AKT, RAF1 and PIM1. Dudek et al. (Dudek, H.; Datta, S. R.; Franke, T. F.; Birnbaum, M. J.; Yao, R.; Cooper, G. M.; Segal, R. A.; Kaplan, D. R.; Greenberg, M. E.: Regulation of neuronal survival by the serine-threonine protein kinase Akt. Science 275: 661-663, 1997) demonstrated that AKT is important for the survival of cerebellar neurons. Thus, the 'orphan' kinase moved center stage as a crucial regulator of life and death decisions emanating from the cell membrane. Holland et al. (Holland, E. C.; Celestino, J.; Dai, C.; Schaefer, L.; Sawaya, R. E.; Fuller, G. N.: Combined activation of Ras and Akt in neural progenitors induces glioblastoma formation in mice. Nature Genet. 25: 55-57, 2000.) transferred, in a tissue-specific manner, genes encoding activated forms of Ras and Akt to astrocytes and neural progenitors in mice. These authors found that although neither activated Ras nor Akt alone was sufficient to induce glioblastoma multiforme (GBM) formation, the combination of activated Ras and Akt induced high-grade gliomas with the histologic features of human GBMs. These tumors appeared to arise after gene transfer to neural progenitors, but not after transfer to differentiated astrocytes. Increased activity of Ras is found in many human GBMs and Akt activity is increased in most of these tumors, implying that combined activation of these 2 pathways accurately models the biology of this disease (Holland, E. C.; Celestino, J.; Dai, C.; Schaefer, L.; Sawaya, R. E.; Fuller, G. N.: Combined activation of Ras and Akt in neural progenitors induces glioblastoma formation in mice. Nature Genet. 25: 55-57, 2000.).

Another disease that involves yet another serine/threonine kinase is Peutz-Jeghers syndrome (PJS) , an autosomal dominant disorder characterized by melanocytic macules of the lips, buccal mucosa, and digits, multiple gastrointestinal hamartomatous polyps, and an increased risk of various neoplasms. Jenne et al. (Jenne, D. E.; Reimann, H.; Nezu, J.; Friedel,

W.; Loff, S.; Jeschke, R.; Muller, O.; Back, W.; Zimmer, M. : Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. Nature Genet. 18: 38-43, 1998.) identified and characterized the serine/threonine kinase STK11 and identified mutations in PJS patients. All 5 germline mutations were predicted to disrupt the function of the kinase domain. They concluded that germline mutations in STK11, probably in conjunction with acquired genetic defects of the second allele in somatic cells according to the Knudson model, caused the manifestations of PJS. These authors commented that PJS was the first cancer susceptibility syndrome identified that is due to inactivating mutations in a protein kinase and found mutations in the STK11 gene in 11 of 12 unrelated families with PJS. Ten of the 11 were truncating mutations. All were heterozygous in the germline. Su et al. found that of 53 PJS patients with cancer reported to that time, 6 (11%) were diagnosed with pancreatic adenocarcinoma. Su et al. (Su, J.-Y.; Erikson, E.; Maller, J. L.: Cloning and characterization of a novel serine/threonine protein kinase expressed in early Xenopus embryos. J. Biol. Chem. 271: 14430-14437, 1996) presented evidence that the STK11 gene plays a role in the development of both sporadic and familial (PJS) pancreatic and biliary cancers. They found that in sporadic cancers, the STK11 gene was somatically mutated in 5% of pancreatic cancers and in at least 6% of biliary cancers examined. In the patient with pancreatic cancer associated with PJS, there was inheritance of a mutated copy of the STK11 gene and somatic loss of the remaining wildtype allele.

The disclosed NOV5 nucleic acid of the invention encoding a Serin/threonine kinase -like protein includes the nucleic acid whose sequence is provided in Table 5A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 5A while still encoding a protein that maintains its Serin/threonine kinase -like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 1 percent of the bases may be so changed.

The disclosed NOV5a protein of the invention includes the Serin/threonine kinase -like protein whose sequence is provided in Table 5B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 5B while still encoding a protein that maintains its Serin/threonine kinase-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 1 percent of the residues may be so changed.

The NOV5 nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in various diseases, disorders and conditions. The NOV5 nucleic acid, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV5 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV5a protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV5a epitope is from about amino acids 120 to 160. In other embodiments, NOV5a epitope is from about amino acids 260 to 280, from about amino acids 310 to 330 and from about amino acids 660 to 690. This novel protein also has value in development of powerful assay system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV6

NOV6 includes four novel TGF-beta binding protein-like proteins disclosed below. The disclosed sequences have been named NOV6a, NOV6b, NOV6c and NOV6d..

NOV6a

A disclosed NOV6a nucleic acid of 4818 nucleotides (also referred to as CG50215-01) encoding a novel TGF-beta binding protein-like protein is shown in Table 6A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 137-139 and ending with a TGA codon at nucleotides 4544-4546.

Table 6A. NOV6a Nucleotide Sequence (SEQ ID NO:25)

CGGGCGGCGTGCGGCTGCTCTGGGTGTCGCTATTGGTGCTGCTGGCGCAGCTAGGGGCCGCAGCCTGGACTGGGCCGGCT
CGGAGAGCGTCTCCGCGTGCGCTTCACCCCGGTCGTGTGCGGCCTGCGCTGCGTCCATGGGCCGACCGGCTCCCGCTGTA
CCCCGACCTGCGCGCCCCGCAACGCCACCAGCGTGGACAGCGGCGCTCCCGGCGGGGCGGCCCCGGGGGGACCCGGGCTT
CCGCGCCTTCCTGTGTCCCTTGATCTGTCACAATGGCGGTGTGTGCGTGAAGCCTGACCGCTGCCTCTGTCCCCCGGACT
TCGCTGGCAAGTTCTGCCAGTTGCACTCCTCGGGCGCCCGGCCCCCGGCCCCGGCTATACCAGGCCTCACCCGCTCCGTG
TACACTATGCCACTGGCCAACCACCGCGACGACGAGCACGGCGTGGCATCTATGGTGAGCGTCCACGTGGAGCACCCGCA
GGAGGCGTCGGTGGTGGTGCACCAGGTGGAGCGTGTGTCTGGCCCTTGGGAGGAGGCGGACGCTGAGGCGGTGGCGCGGG
CGGAAGCGGCGGCGCGGGCGGAGGCGGCAGCGCCCTACACGGTGTTGGCACAGAGCGCGCCGCGGGAGGACGGCTACTCA
GATGCCTCGGGCTTCGGTTACTGCTTTCGGGAGCTGCGCGGAGGCGAATGCGCGTCCCCGCTGCCCGGGCTCCGGACGCA
GGAGGTCTGCTGCCGAGGGGCCGGCTTGGCCTGGGGCGTTCACGACTGTCAGCTGTGCTCCGAGCGCCTGGGGAACTCCG
AAAGAGTGAGCGCCCCAGATGGACCTTGTCCAACCGGCTTTGAAAGAGTTAATGGGTCCTGCGAAGATGTGGATGAGTGC
GCGACTGGCGGGCGCTGCCAGCACGGCGAGTGTGCAAACACGCGCGGCGGGTACACGTGTGTGTGCCCCGACGGCTTTCT
GCTCGACTCGTCCCGCAGCAGCTGCATCTCCCAACACGTGATCTCAGAGGCCAAAGGGCCCTGCTTCCGCGTGCTCCGCG
ACGGCGGCTGTTCGCTGCCCATTCTGCGGAACATCACTAAACAGATCTGCTGCTGCAGCCGCGTAGGCAAGGCCTGGGGC
CGGGGCTGCCAGCTCTGCCCACCCTTCGGCTCAGAGGGTTTCCGGGAGATCTGCCCGGCTGGTCCTGGTTACCACTACTC
GGCCTCCGACCTCCGCTACAACACCAGACCCCTGGGCCAGGAGCCACCCCGAGTGTCACTCAGCCAGCCTCGTACCCTGC
CAGCCACCTCTCGGCCATCTGCAGGCTTTCTGCCCACCCATCGCCTGGAGCCCCGGCCTGAACCCCGGCCCGATCCCCGG
CCCGGCCCTGAGTTTCCCTTGCCCAGCATCCCTGCCTGGACTGGTCCTGAGATTCCTGAATCAGGTCCTTCCTCCGGCAT
GTGTCAGCGCAACCCCCAGGTCTGCGGCCCAGGACGCTGCATTTCCCGGCCCAGCGGCTACACCTGCGCTTGCGACTCTG
GCTTCCGGCTCAGCCCCCAGGGCACCCGATGCATTGATGTGGACGAATGTCGCCGCGTGCCCCCGCCCTGTGCTCCCGGG
CGCTGCGAGAACTCACCAGGCAGCTTCCGCTGCGTGTGCGGCCCGGGCTTCCGAGCCGGCCCACGGGCTGCGGAATGCCT
GGATGTGGACGAGTGCCACCGCGTGCCGCCGCCGTGTGACCTCGGGCGCTGCGAGAACACGCCAGGCAGCTTCCTGTGCG
TGTGCCCCGCCGGGTACCAGGCTGCACCGCACGGAGCCAGCTGCCAGGATGTGGATGAATGCACCCAGAGCCCAGGCCTG
TGTGGCCGAGGGGCCTGCAAGAACCTGCCTGGCTCTTTCCGCTGTGTTTGCCCGGCTGGCTTCCGGGGCTCGGCGTGTGA
AGAGGATGTGGATGAGTGTGCCCAGGAGCCGCCGCCCTGTGGGCCCGGCCGCTGTGACAACACGGCAGGCTCCTTTCACT
GTGCCTGCCCTGCTGGCTTCCGCTCCCGAGGGCCCGGGGCCCCCTGCCAAGATGTGGATGAGTGTGCCCGAAGCCCCCA
CCCTGCACCTACGGCCGGTGTGAGAACACAGAAGGCAGCTTCCAGTGTGTCTGCCCCATGGGCTTCCAACCCAACGCTGC
TGGCTCCGAGTGCGAGGATGTGGATGAGTGTGAGAACCACCTCGCATGCCCTGGGCAGGAGTGTGTGAACTCGCCCGGCT
CCTTCCAGTGCAGGGCCTGTCCTTCTGGCCACCACCTGCACCGTGGCAGATGCACTGATGTGGACGAATGCAGTTCGGGT
GCCCCTCCCTGTGGTCCCCACGGCCACTGCACTAACACCGAAGGCTCCTTCCGCTGCAGCTGCGCGCCAGGCTACCGGGC
GCCGTCGGGTCGGCCCGGGCCCTGCGCAGACGTGAACGAGTGCCTGGAGGGCGATTTCTGCTTCCCTCACGGCGAGTGCC
TCAACACTGACGGCTCCTTTGCCTGTACTTGTGCCCCTGGCTACCGACCCGGACCCCGCGGAGCCTCTTGCCTCGACGTT
GACGAGTGCAGCGAGGAGGACCTTTGCCAGAGCGGCATCTGTACCAACACCGACGGCTCCTTCGAGCGCATCTGTCCTCC
GGGACACCGCGCTGGCCCGGACCTCGCCTCCTGCCTCGACGTGGACGAATGTCGCGAGCGAGGCCCAGCCCTGTGCGGGT
CGCAGCGCTGTGAGAACTCTCCCGGCTCCTACCGCTGTGTCCGGGACTGCGATCCTGGGTACCACGCGGGCCCCGAGGGC
ACCTGTGACGATGTGGATGAGTGCCAAGAATATGGTCCCGAGATTTGTGGAGCCCAGCGTTGTGAGAACACCCCTGGCTC
CTACCGCTGCACACCAGCCTGTGACCCTGGCTATCAGCCCACGCCAGGGGGCGGATGCCAGGATGTGAACGAGTGTGAAA
CACTACAGGGTGTATGTGGAGCTGCCCTGTGTGAAAATGTCGAAGGCTCCTTCCTCTGTGTCTGCCCCAACAGCCCGGAA
GAGTTTGACCCCATGACTGGACGCTGTGTTCCCCCACGAACTTCTGCTGGCACGTTCCCAGGCTCGCAGCCCCAGGCACC
TGCTAGCCCCGTTCTGCCCGCCAGGCCACCTCCGCCACCCCTGCCCCGCCGACCCAGCACACCTAGGCAGGGCCCTGTGG
GGAGTGGGCGCCGGGAGTGCTACTTTGACACAGCGGCCCCGGATGCATGTGACAACATCCTGGCTCGGAATGTGACATGG
CAGGAGTGCTGCTGTACTGTGGGTGAGGGCTGGGGCAGCGGCTGCCGCATCCAGCAGTGCCCGGGCACCGAGACAGCTGA
GTACCAGTCATTGTGCCCTCACGGCCGGGGCTACCTGGCGCCCAGTGGAGACCTGAGCCTCCGGAGAGACGTGGACGAAT
GTCAGCTCTTCCGAGACCAGGTGTGCAAGAGTGGCGTGTGTGTGAACACGGCCCCGGGCTACTCATGCTATTGCAGCAAC
GGCTACTACTACCACACACAGCGGCTGGAGTGCATCGACAATGACGAGTGCGCCGATGAGGAACCGGCCTGTGAGGGCGG
CCGCTGTGTCAACACTGTGGGCTCTTATCACTGTACCTGCGAGCCCCCACTGGTGCTGGATGGCTCGCAGCGCCGCTGCG
TCTCCAACGAGAGCCAGAGCCTCGATGACAATCTGGGAGTCTGCTGGCAGGAAGTGGGGGCTGACCTCGTGTGCAGCCAC
CCTCGGCTGGACTGTCAGGCCACCTACACAGAGTGCTGCTGCCTGTATGGAGAGGCCTGGGGCATGGACTGCGCCCTCTG
CCCTGCGCAGGACTCAGATGACTTCGAGGCCCTGTGCAATGTGCTACGCCCCCCCGCATATAGCCCCCCGCGACCAGGTG
GCTTTGGACTCCCCTACGAGTACGGCCCAGACTTAGGTCCACCTTACCAGGGCCTCCCATATGGGCCTGAGTTGTACCCA
CCACCTGCGCTACCCTACGACCCCTACCCACCGCCACCTGGGCCCTTCGCCCGCCGGGAGGCTCCTTATGGGGCACCCCG
CTTCGACATGCCAGACTTTGAGGACGATGGTGGCCCCTATGGCGAATCTGAGGCTCCTGCGCCACCTGGCCCGGGCACCC
GCTGGCCCTATCGGTCCCGGGACACCCGCCGCTCCTTCCCAGAGCCCGAGGAGCCTCCTGAAGGTGGAAGCTATGCTGGT
TCCCTGGCTGAGCCCTACGAGGAGCTGGAGGCCGAGGAGTGCGGGATCCTGGACGGCTGCACCAACGGCCGCTGCGTGCG
CGTCCCCGAAGGCTTCACCTGCCGTTGCTTCGACGGCTACCGCCTGGACATGACCCGCATGGCCTGCGTTGACATCAACG
AGTGTGATGAGGCCGAGGCTGCCTCCCCGCTGTGCGTCAACGCGCGTTGCCTCAACACGGATGGCTCCTTCCGCTGCATC
TGCCGCCCAGGATTTGCACCCACGCACCAGCCACACCACTGTGCGCCCGCACGACCCCGGGCCTGAGCCCTGGCACCCGA
TGGCCACCCACCCGCGCCCGCCACTCGGGGCCCCTGCCCCGCATCCTGCAGCCCGCTTAGTCTGATGACGAGGAAGCCCG
CCAGAAAGTCCAGAAGAAGGAACGACGGACGCAAAGCGGCGCCGCCTACCATGCCTCCCCCCCCCACCACCACCCCCCCC
AACTGTGGTCGTCCCCGCCCGGCCCACCCCGCCCCCATTTCTCCCCCCTTCTTTCAATAAAAATTTCAATCATAAAAAAC
CACCTATAAAAAAAAAAA

The disclosed NOV6a nucleic acid sequence, which is mapped to chromosome 19q13.1-13.2, has has 2989 of 3024 bases (98%) identical to a gb:GENBANK-

ID:AF051344|acc:AF051344.1 mRNA from Homo sapiens (Homo sapiens latent transforming growth factor-beta binding protein 4S mRNA, complete cds).

A disclosed NOV6a polypeptide (SEQ ID NO:22) encoded by SEQ ID NO:21 is 1469 amino acid residues and is presented using the one-letter amino acid code in Table 6B. Signal P, Psort and/or Hydropathy results predict that NOV6a contains no signal peptide and is likely to be localized in the cytoplasm with a certainty of 0.6500. In other embodiments, NOV6a is also likely to be localized to the mitochondrial matrix space with a certainty of 0.1000, or the lysosome (lumen) with a certainty of 0.1000.

Table 6B. Encoded NOV6a protein sequence (SEQ ID NO:26).

```
MGRPAPAVPRPARPATPPAWTAALPAGRPRGDPGFRAFLCPLICHNGGVCVKPDRCLCPPDFAGKFCQLH
SSGARPPAPAIPGLTRSVYTMPLANHRDDEHGVASMVSVHVEHPQEASVVVHQVERVSGPWEEADAEAVA
RAEAAARAEAAAPYTVLAQSAPREDGYSDASGFGYCFRELRGGECASPLPGLRTQEVCCRGAGLAWGVHD
CQLCSERLGNSERVSAPDGPCPTGFERVNGSCEDVDECATGGRCQHGECANTRGGYTCVCPDGFLLDSSR
SSCISQHVISEAKGPCFRVLRDGGCSLPILRNITKQICCCSRVGKAWGRGCQLCPPFGSEGFREICPAGP
GYHYSASDLRYNTRPLGQEPPRVSLSQPRTLPATSRPSAGFLPTHRLEPRPEPRPDPRPGPEFPLPSIPA
WTGPEIPESGPSSGMCQRNPQVCGPGRCISRPSGYTCACDSGFRLSPQGTRCIDVDECRRVPPPCAPGRC
ENSPGSFRCVCGPGFRAGPRAAECLDVDECHRVPPPCDLGRCENTPGSFLCVCPAGYQAAPHGASCQDVD
ECTQSPGLCGRGACKNLPGSFRCVCPAGFRGSACEEDVDECAQEPPPCGPGRCDNTAGSFHCACPAGFRS
RGPGAPCQDVDECARSPPPCTYGRCENTEGSFQCVCPMGFQPNAAGSECEDVDECENHLACPGQECVNSP
GSFQCRACPSGHHLHRGRCTDVDECSSGAPPCGPHGHCTNTEGSFRCSCAPGYRAPSGRPGPCADVNECL
EGDFCFPHGECLNTDGSFACTCAPGYRPGPRGASCLDVDECSEEDLCQSGICTNTDGSFERICPPGHRAG
PDLASCLDVDECRERGPALCGSQRCENSPGSYRCVRDCDPGYHAGPEGTCDDVDECQEYGPEICGAQRCE
NTPGSYRCTPACDPGYQPTPGGGCQDVNECETLQGVCGAALCENVEGSFLCVCPNSPEEFDPMTGRCVPP
RTSAGTFPGSQPQAPASPVLPARPPPPPLPRRPSTPRQGPVGSGRRECYFDTAAPDACDNILARNVTWQE
CCCTVGEGWGSGCRIQQCPGTETAEYQSLCPHGRGYLAPSGDLSLRRDVDECQLFRDQVCKSGVCVNTAP
GYSCYCSNGYYYHTQRLECIDNDECADEEPACEGGRCVNTVGSYHCTCEPPLVLDGSQRRCVSNESQSLD
DNLGVCWQEVGADLVCSHPRLDCQATYTECCCLYGEAWGMDCALCPAQDSDDFEALCNVLRPPAYSPPRP
GGFGLPYEYGPDLGPPYQGLPYGPELYPPPALPYDPYPPPPGPFARREAPYGAPRFDMPDFEDDGGPYGE
SEAPAPPGPGTRWPYRSRDTRRSFPEPEEPPEGGSYAGSLAEPYEELEAEECGILDGCTNGRCVRVPEGF
TCRCFDGYRLDMTRMACVDINECDEAEAASPLCVNARCLNTDGSFRCICRPGFAPTHQPHHCAPARPRA
```

The disclosed NOV6a amino acid sequence has 950 of 968 amino acid residues (98%) identical to, and 956 of 968 amino acid residues (98%) similar to, the 1511 amino acid residue ptnr:SPTREMBL-ACC:O75412 protein from Homo sapiens (Human) (LATENT TRANSFORMING GROWTH FACTOR-BETA BINDING PROTEIN 4S).

NOV6a is expressed in Adrenal gland, bone marrow, brain - amygdala, brain - cerebellum, brain - hippocampus, brain - substantia nigra, brain - thalamus, brain -whole, fetal brain, fetal kidney, fetal liver, fetal lung, heart, kidney, lymphoma - Raji, mammary gland, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thyroid, trachea, uterus, Bone, Cervix, Lung, and Ovary.

NOV6b

A disclosed NOV6b nucleic acid of 4812 nucleotides (also referred to as CG50215-03) encoding a novel TGF-beta binding protein-like protein is shown in Table 6A. An open

reading frame was identified beginning with an ATG initiation codon at nucleotides 137-139 and ending with a TGA codon at nucleotides 4538-4540. A putative untranslated region upstream from the initiation codon and downstream from the termination codon is underlined in Table 6A, and the start and stop codons are in bold letters.

Table 6C. NOV6b Nucleotide Sequence (SEQ ID NO:27)

CGGGCGGCGTGCGGCTGCTCTGGGTGTCGCTATTGGTGCTGCTGGCGCAGCTAGGGGCCG
CAGCCTGGACTGGGCCGGCTCGGAGAGCGTCTCCGCGTGCGCTTCACCCCGGTCGTGTGC
GGCCTGCGCTGCGTCC**ATG**GGCCGACCGGCTCCCGCTGTACCCCGACCTGCGCGCCCCGC
AACGCCACCAGCGTGGACAGCGGCGCTCCCGGCGGGGCGGCCCCGGGGGGACCCGGGCTT
CCGCGCCTTCCTGTGTCCCTTGATCTGTCACAATGGCGGTGTGTGCGTGAAGCCTGACCG
CTGCCTCTGTCCCCCGGACTTCGCTGGCAAGTTCTGCCAGTTGCACTCCTCGGGCGCCCG
GCCCCCGGCCCCGGCTATACCAGGCCTCACCCGCTCCGTGTACACTATGCCACTGGCCAA
CCACCGCGACGACGAGCACGGCGTGGCATCTATGGTGAGCGTCCACGTGGAGCACCCGCA
GGAGGCGTCGGTGGTGGTGCACCAGGTGGAGCGTGTGTCTGGCCCTTGGGAGGAGGCGGA
CGCTGAGGCGGTGGCGCGGGCGGAAGCGGCGGCGCGGGCGGAGGCGGCAGCGCCCTACAC
GGTGTTGGCACAGAGCGCGCCGCGGGAGGACGGCTACTCAGATGCCTCGGGCTTCGGTTA
CTGCTTTCGGGAGCTGCGCGGAGGCGAATGCGCGTCCCCGCTGCCCGGGCTCCGGACGCA
GGAGGTCTGCTGCCGAGGGGCCGGCTTGGCCTGGGGCGTTCACGACTGTCAGCTGTGCTC
CGAGCGCCTGGGGAACTCCGAAAGAGTGAGCGCCCCAGATGGACCTTGTCCAACCGGCTT
TGAAAGAGTTAATGGGTCCTGCGAAGATGTGGATGAGTGCGCGACTGGCGGGCGCTGCCA
GCACGGCGAGTGTGCAAACACGCGCGGCGGGTACACGTGTGTGTGCCCCGACGGCTTTCT
GCTCGACTCGTCCCGCAGCAGCTGCATCTCCCAACACGTGATCTCAGAGGCCAAAGGGCC
CTGCTTCCGCGTGCTCCGCGACGGCGGCTGTTCGCTGCCCATTCTGCGGAACATCACTAA
ACAGATCTGCTGCTGCAGCCGCGTAGGCAAGGCCTGGGGCCGGGGCTGCCAGCTCTGCCC
ACCCTTCGGCTCAGAGGGTTTCCGGGAGATCTGCCCGGCTGGTCCTGGTTACCACTACTC
GGCCTCCGACCTCCGCTACAACACCAGACCCCTGGGCCAGGAGCCACCCCGAGTGTCACT
CAGCCAGCCTCGTACCCTGCCAGCCACCTCTCGGCCATCTGCAGGCTTTCTGCCCACCCA
TCGCCTGGAGCCCCGGCCTGAACCCCGGCCCGATCCCCGGCCCGGCCCTGAGTTTCCCTT
GCCCAGCATCCCTGCCTGGACTGGTCCTGAGATTCCTGAATCAGGTCCTTCCTCCGGCAT
GTGTCAGCGCAACCCCCAGGTCTGCGGCCCAGGACGCTGCATTTCCCGGCCCAGCGGCTA
CACCTGCGCTTGCGACTCTGGCTTCCGGCTCAGCCCCCAGGGCACCCGATGCATTGATGT
GGACGAATGTCGCCGCGTGCCCCCGCCCTGTGCTCCCGGGCGCTGCGAGAACTCACCAGG
CAGCTTCCGCTGCGTGTGCGGCCCGGGCTTCCGAGCCGGCCCACGGGCTGCGGAATGCCT
GGATGTGGACGAGTGCCACCGCGTGCCGCCGCCGTGTGACCTCGGGCGCTGCGAGAACAC
GCCAGGCAGCTTCCTGTGCGTGTGCCCCGCCGGGTACCAGGCTGCACCGCACGGAGCCAG
CTGCCAGGATGTGGATGAATGCACCCAGAGCCCAGGCCTGTGTGGCCGAGGGGCCTGCAA
GAACCTGCCTGGCTCTTTCCGCTGTGTTTGCCCGGCTGGCTTCCGGGGCTCGGCGTGTGA
AGAGGATGTGGATGAGTGTGCCCAGGAGCCGCCGCCCTGTGGGCCCGGCCGCTGTGACAA
CACGGCAGGCTCCTTTCACTGTGCCTGCCCTGCTGGCTTCCGCTCCCGAGGGCCCGGGGC
CCCCTGCCAAGATGTGGATGAGTGTGCCCGAAGCCCCCCACCCTGCACCTACGGCCGGTG
TGAGAACACAGAAGGCAGCTTCCAGTGTGTCTGCCCCATGGGCTTCCAACCCAACGCTGC
TGGCTCCGAGTGCGAGGATGTGGATGAGTGTGAGAACCACCTCGCATGCCCTGGGCAGGA
GTGTGTGAACTCGCCCGGCTCCTTCCAGTGCAGGGCCTGTCCTTCTGGCCACCACCTGCA
CCGTGGCAGATGCACTGATGTGGACGAATGCAGTTCGGGTGCCCCTCCCTGTGGTCCCCA
CGGCCACTGCACTAACACCGAAGGCTCCTTCCGCTGCAGCTGCGCGCCAGGCTACCGGGC
GCCGTCGGGTCGGCCCGGGCCCTGCGCAGACGTGAACGAGTGCCTGGAGGGCGATTTCTG
CTTCCCTCACGGCGAGTGCCTCAACACTGACGGCTCCTTTGCCTGTACTTGTGCCCCTGG
CTACCGACCCGGACCCCGCGGAGCCTCTTGCCTCGACGTTGACGAGTGCAGCGAGGAGGA
CCTTTGCCAGAGCGGCATCTGTACCAACACCGACGGCTCCTTCGAGTGCATCTGTCCTCC
GGGACACCGCGCTGGCCCGGACCTCGCCTCCTGCCTCGACGTGGACGAATGTCGCGAGCG
AGGCCCAGCCCTGTGCGGGTCGCAGCGCTGTGAGAACTCTCCCGGCTCCTACCGCTGTGT
CCGGGACTGCGATCCTGGGTACCACGCGGGCCCCGAGGGCACCTGTGACGATGTGGACGA
ATGCCGGAACCGGTCCTTCTGCGGTGCCCACGCCGTGTGCCAGAACCTGCCCGGCTCCTT
CCAGTGCCTCTGTGACCAGGGTTACGAGGGGGCACGGGATGGGCGTCACTGCGTGGATGT
GAACGAGTGTGAAACACTACAGGGTGTATGTGGAGCTGCCCTGTGTGAAAATGTCGAAGG
CTCCTTCCTCTGTGTCTGCCCCAACAGCCCGGAAGAGTTTGACCCCATGACTGGACGCTG
TGTTCCCCCACGAACTTCTGCTGGCACGTTCCCAGGCTCGCAGCCCCAGGCACCTGCTAG
CCCCGTTCTGCCCGCCAGGCCACCTCCGCCACCCCTGCCCCGCCGACCCAGCACACCTAG
GCAGGGCCCTGTGGGGAGTGGGCGCCGGGAGTGCTACTTTGACACAGCGGCCCCGGATGC
ATGTGACAACATCCTGGCTCGGAATGTGACATGGCAGGAGTGCTGCTGTACTGTGGGTGA
GGGCTGGGGCAGCGGCTGCCGCATCCAGCAGTGCCCGGGCACCGAGACAGCTGAGTACCA
GTCATTGTGCCCTCACGGCCGGGGCTACCTGGCGCCCAGTGGAGACCTGAGCCTCCGGAG

AGACGTGGACGAATGTCAGCTCTTCCGAGACCAGGTGTGCAAGAGTGGCGTGTGTGTGAA
CACGGCCCCGGGCTACTCATGCTATTGCAGCAACGGCTACTACTACCACACACAGCGGCT
GGAGTGCATCGACAATGACGAGTGCGCCGATGAGGAACCGGCCTGTGAGGGCGGCCGCTG
TGTCAACACTGTGGGCTCTTATCACTGTACCTGCGAGCCCCCACTGGTGCTGGATGGCTC
GCAGCGCCGCTGCGTCTCCAACGAGAGCCAGAGCCTCGATGACAATCTGGGAGTGTGCTG
GCAGGAAGTGGGGGCTGACCTCGTGTGCAGCCACCCTCGGCTGGACCGTCAGGCCACCTA
CACAGAGTGCTGCTGCCTGTATGGAGAGGCCTGGGGCATGGACTGCGCCCTCTGCCCTGC
GCAGGACTCAGATGACTTCGAGGCCCTGTGCAATGTGCTACGCCCCCCCGCATATAGCCC
CCCGCGACCAGGTGGCTTTGGACTCCCCTACGAGTACGGCCCAGACTTAGGTCCACCTTA
CCAGGGCCTCCCATATGGGCCTGAGTTGTACCCACCACCTGCGCTACCCTACGACCCCTA
CCCACCGCCACCTGGGCCCTTCGCCCGCCGGGAGGCTCCTTATGGGGCACCCCGCTTCGA
CATGCCAGACTTTGAGGACGATGGTGGCCCCTATGGCGAATCTGAGGCTCCTGCGCCACC
TGGCCCGGGCACCCGCTGGCCCTATCGGTCCCGGGACACCCGCCGCTCCTTCCCAGAGCC
CGAGGAGCCTCCTGAAGGTGGAAGCTATGCTGGTTCCCTGGCTGAGCCCTACGAGGAGCT
GGAGGCCGAGGAGTGCGGGATCCTGGACGGCTGCACCAACGGCCGCTGCGTGCGCGTCCC
CGAAGGCTTCACCTGCCGTTGCTTCGACGGCTACCGCCTGGACATGACCCGCATGGCCTG
CGTTGACATCAACGAGTGTGATGAGGCCGAGGCTGCCTCCCCGCTGTGCGTCAACGCGCG
TTGCCTCAACACGGATGGCTCCTTCCGCTGCATCTGCCGCCCAGGATTTGCACCCACGCA
CCAGCCACACCACTGTGCGCCCGCACGACCCCGGGCC**TGA**GCCCTGGCACCCGATGGCCA
CCCACCCGCGCCCGCCACTCGGGGCCCCTGCCCCGCATCCTGCAGCCCGCTTAGTCTGAT
GACGAGGAAGCCCGCCAGAAAGTCCAGAAGAAGGAACGACGGACGCAAAGCGGCGCCGCC
TACCATGCCTCCCCCCCCCACCACCACCCCCCCCAACTGTGGTCGTCCCCGCCCGGCCCA
CCCCGCCCCCATTTCTCCCCCCTTCTTTCAATAAAAATTTCAATCATAAAAAACCACCTA
TAAAAAAAAAAA

PCR cloning of a NOV6b nucleic acid is disclosed in Example 4.

The disclosed NOV6b nucleic acid sequence, which maps to chromosome 19 has 2940 of 3024 bases (97%) identical to a gb:GENBANK-ID:AF051344|acc:AF051344.1 mRNA from Homo sapiens (Homo sapiens latent transforming growth factor-beta binding protein 4S mRNA, complete cds).

A disclosed NOV6b polypeptide (SEQ ID NO:22) encoded by SEQ ID NO:21 is 1467 amino acid residues and is presented using the one-letter amino acid code in Table 6B. Signal P, Psort and/or Hydropathy results predict that NOV6b contains no signal peptide and is likely to be localized in the cytoplasm with a certainty of 0.6500. In other embodiments, NOV6b is also likely to be localized to the mitochondrial matrix space with a certainty of 0.1000, or the lysosome (lumen) with a certainty of 0.1000.

Table 6D. Encoded NOV6b protein sequence (SEQ ID NO:28).

MGRPAPAVPRPARPATPPAWTAALPAGRPRGDPGFRAFLCPLICHNGGVCVKPDRCLCPP
DFAGKFCQLHSSGARPPAPAIPGLTRSVYTMPLANHRDDEHGVASMVSVHVEHPQEASVV
VHQVERVSGPWEEADAEAVARAEAAARAEAAAPYTVLAQSAPREDGYSDASGFGYCFREL
RGGECASPLPGLRTQEVCCRGAGLAWGVHDCQLCSERLGNSERVSAPDGPCPTGFERVNG
SCEDVDECATGGRCQHGECANTRGGYTCVCPDGFLLDSSRSSCISQHVISEAKGPCFRVL
RDGGCSLPILRNITKQICCCSRVGKAWGRGCQLCPPFGSEGFREICPAGPGYHYSASDLR
YNTRPLGQEPPRVSLSQPRTLPATSRPSAGFLPTHRLEPRPEPRPDPRPGPEFPLPSIPA
WTGPEIPESGPSSGMCQRNPQVCGPGRCISRPSGYTCACDSGFRLSPQGTRCIDVDECRR
VPPPCAPGRCENSPGSFRCVCGPGFRAGPRAAECLDVDECHRVPPPCDLGRCENTPGSFL
CVCPAGYQAAPHGASCQDVDECTQSPGLCGRGACKNLPGSFRCVCPAGFRGSACEEDVDE
CAQEPPPCGPGRCDNTAGSFHCACPAGFRSRGPGAPCQDVDECARSPPPCTYGRCENTEG
SFQCVCPMGFQPNAAGSECEDVDECENHLACPGQECVNSPGSFQCRACPSGHHLHRGRCT
DVDECSSGAPPCGPHGHCTNTEGSFRCSCAPGYRAPSGRPGPCADVNECLEGDFCFPHGE
CLNTDGSFACTCAPGYRPGPRGASCLDVDECSEEDLCQSGICTNTDGSFECICPPGHRAG
PDLASCLDVDECRERGPALCGSQRCENSPGSYRCVRDCDPGYHAGPEGTCDDVDECRNRS

FCGAHAVCQNLPGSFQCLCDQGYEGARDGRHCVDVNECETLQGVCGAALCENVEGSFLCV
CPNSPEEFDPMTGRCVPPRTSAGTFPGSQPQAPASPVLPARPPPPPLPRRPSTPRQGPVG
SGRRECYFDTAAPDACDNILARNVTWQECCCTVGEGWGSGCRIQQCPGTETAEYQSLCPH
GRGYLAPSGDLSLRRDVDECQLFRDQVCKSGVCVNTAPGYSCYCSNGYYYHTQRLECIDN
DECADEEPACEGGRCVNTVGSYHCTCEPPLVLDGSQRRCVSNESQSLDDNLGVCWQEVGA
DLVCSHPRLDRQATYTECCCLYGEAWGMDCALCPAQDSDDFEALCNVLRPPAYSPPRPGG
FGLPYEYGPDLGPPYQGLPYGPELYPPPALPYDPYPPPPGPFARREAPYGAPRFDMPDFE
DDGGPYGESEAPAPPGPGTRWPYRSRDTRRSFPEPEEPPEGGSYAGSLAEPYEELEAEEC
GILDGCTNGRCVRVPEGFTCRCFDGYRLDMTRMACVDINECDEAEAASPLCVNARCLNTD
GSFRCICRPGFAPTHQPHHCAPARPRA

The disclosed NOV6b amino acid sequence has 927 of 968 amino acid residues (95%) identical to, and 938 of 968 amino acid residues (96%) similar to, the 1511 amino acid residue ptnr:SPTREMBL-ACC:O75412 protein from Homo sapiens (Human) (LATENT TRANSFORMING GROWTH FACTOR-BETA BINDING PROTEIN 4S).

NOV6b is expressed in heart, lung. Expression information was derived from the tissue sources of the sequences that were included in the derivation of the sequence of CuraGen Acc. No. CG50215-03. NOV6b is predicted to be expressed in the following tissues because of the expression pattern of (GENBANK-ID: gb:GENBANK-ID:AF051344|acc:AF051344.1) a closely related Homo sapiens latent transforming growth factor-beta binding protein 4S mRNA: heart, lung, aorta, uterus, and small intestine.

NOV6c

A disclosed NOV6c nucleic acid of 4479 nucleotides (also referred to as CG50215-04) encoding a novel TGF-beta binding protein-like protein is shown in Table 6A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 137-139 and ending at a TGA at nucleotides 4205-4207. A putative untranslated region upstream from the initiation codon and downstream from the termination codon is underlined in Table 6A, and the start and stop codons are in bold letters.

Table 6E. NOV6c Nucleotide Sequence (SEQ ID NO:29)

CGGGCGGCGTGCGGCTGCTCTGGGTGTCGCTATTGGTGCTGCTGGCGCAGCTAGGGGCCG
CAGCCTGGACTGGGCCGGCTCGGAGAGCGTCTCCGCGTGCGCTTCACCCCGGTCGTGTGC
GGCCTGCGCTGCGTCC**ATG**GGCCGACCGGCTCCCGCTGTACCCCGACCTGCGCGCCCCGC
AACGCCACCAGCGTGGACAGCGGCGCTCCCGGCGGGGCGGCCCCGGGGGGACCCGGGCTT
CCGCGCCTTCCTGTGTCCCTTGATCTGTCACAATGGCGGTGTGTGCGTGAAGCCTGACCG
CTGCCTCTGTCCCCCGGACTTCGCTGGCAAGTTCTGCCAGTTGCACTCCTCGGGCGCCCG
GCCCCCGGCCCCGGCTATACCAGGCCTCACCCGCTCCGTGTACACTATGCCACTGGCCAA
CCACCGCGACGACGAGCACGGCGTGGCATCTATGGTGAGCGTCCACGTGGAGCACCCGCA
GGAGGCGTCGGTGGTGGTGCACCAGGTGGAGCGTGTGTCTGGCCCTTGGGAGGAGGCGGA
CGCTGAGGCGGTGGCGCGGGCGGAAGCGGCGGCGCGGGCGGAGGCGGCAGCGCCCTACAC
GGTGTTGGCACAGAGCGCGCCGCGGGAGGACGGCTACTCAGATGCCTCGGGCTTCGGTTA
CTGCTTTCGGGAGCTGCGCGGAGGCGAATGCGCGTCCCCGCTGCCCGGGCTCCGGACGCA
GGAGGTCTGCTGCCGAGGGGCCGGCTTGGCCTGGGGCGTTCACGACTGTCAGCTGTGCTC
CGAGCGCCTGGGGAACTCCGAAAGAGTGAGCGCCCCAGATGGACCTTGTCCAACCGGCTT

TGAAAGAGTTAATGGGTCCTGCGAAGATGTGGATGAGTGCGCGACTGGCGGGCGCTGCCA
GCACGGCGAGTGTGCAAACACGCGCGGCGGGTACACGTGTGTGTGCCCCGACGGCTTTCT
GCTCGACTCGTCCCGCAGCAGCTGCATCTCCCAACACGTGATCTCAGAGGCCAAAGGGCC
CTGCTTCCGCGTGCTCCGCGACGGCGGCTGTTCGCTGCCCATTCTGCGGAACATCACTAA
ACAGATCTGCTGCTGCAGCCGCGTAGGCAAGGCCTGGGGCCGGGGCTGCCAGCTCTGCCC
ACCCTTCGGCTCAGAGGGTTTCCGGGAGATCTGCCCGGCTGGTCCTGGTTACCACTACTC
GGCCTCCGACCTCCGCTACAACACCAGACCCCTGGGCCAGGAGCCACCCCGAGTGTCACT
CAGCCAGCCTCGTACCCTGCCAGCCACCTCTCGGCCATCTGCAGGCTTTCTGCCCACCCA
TCGCCTGGAGCCCCGGCCTGAACCCCGGCCCGATCCCCGGCCCGGCCCTGAGTTTCCCTT
GCCCAGCATCCCTGCCTGGACTGGTCCTGAGATTCCTGAATCAGGTCCTTCCTCCGGCAT
GTGTCAGCGCAACCCCCAGGTCTGCGGCCCAGGACGCTGCATTTCCCGGCCCAGCGGCTA
CACCTGCGCTTGCGACTCTGGCTTCCGGCTCAGCCCCCAGGGCACCCGATGCATTGATGT
GGACGAATGTCGCCGCGTGCCCCCGCCCTGTGCTCCCGGGCGCTGCGAGAACTCACCAGG
CAGCTTCCGCTGCGTGTGCGGCCCGGGCTTCCGAGCCGGCCCACGGGCTGCGGAATGCCT
GGATGTGGACGAGTGCCACCGCGTGCCGCCGCCGTGTGACCTCGGGCGCTGCGAGAACAC
GCCAGGCAGCTTCCTGTGCGTGTGCCCCGCCGGGTACCAGGCTGCACCGCACGGAGCCAG
CTGCCAGGATGTGGATGAATGCACCCAGAGCCCAGGCCTGTGTGGCCGAGGGGCCTGCAA
GAACCTGCCTGGCTCTTTCCGCTGTGTTTGCCCGGCTGGCTTCCGGGGCTCGGCGTGTGA
AGAGGATGTGGATGAGTGTGCCCAGGAGCCGCCGCCCTGTGGGCCCGGCCGCTGTGACAA
CACGGCAGGCTCCTTTCACTGTGCCTGCCCTGCTGGCTTCCGCTCCCGAGGGCCCGGGGC
CCCCTGCCAAGATGTGGATGAGTGTGCCCGAAGCCCCCCACCCTGCACCTACGGCCGGTG
TGAGAACACAGAAGGCAGCTTCCAGTGTGTCTGCCCCATGGGCTTCCAACCCAACGCTGC
TGGCTCCGAGTGCGAGGATGTGGATGAGTGTGAGAACCACCTCGCATGCCCTGGGCAGGA
GTGTGTGAACTCGCCCGGCTCCTTCCAGTGCAGGGCCTGTCCTTCTGGCCACCACCTGCA
CCGTGGCAGATGCACTGATGTGGACGAATGCAGTTCGGGTGCCCCTCCCTGTGGTCCCCA
CGGCCACTGCACTAACACCGAAGGCTCCTTCCGCTGCAGCTGCGCGCCAGGCTACCGGGC
GCCGTCGGGTCGGCCCGGGCCCTGCGCAGACGTGAACGAGTGCCTGGAGGGCGATTTCTG
CTTCCCTCACGGCGAGTGCCTCAACACTGACGGCTCCTTTGCCTGTACTTGTGCCCCTGG
CTACCGACCCGGACCCCGCGGAGCCTCTTGCCTCGACGTTGACGAGTGCAGCGAGGAGGA
CCTTTGCCAGAGCGGCATCTGTACCAACACCGACGGCTCCTTCGAGCGCATCTGTCCTCC
GGGACACCGCGCTGGCCCGGACCTCGCCTCCTGCCTCGACGTGGACGAATGTCGCGAGCG
AGGCCCAGCCCTGTGCGGGTCGCAGCGCTGTGAGAACTCTCCCGGCTCCTACCGCTGTGT
CCGGGACTGCGATCCTGGGTACCACGCGGGCCCCGAGGGCACCTGTGACGATGTGGATGA
GTGCCAAGAATATGGTCCCGAGATTTGTGGAGCCCAGCGTTGTGAGAACACCCCTGGCTC
CTACCGCTGCACACCAGCCTGTGACCCTGGCTATCAGCCCACGCCAGGGGGCGGATGCCA
GGATGTGAACGAGTGTGAAACACTACAGGGTGTATGTGGAGCTGCCCTGTGTGAAAATGT
CGAAGGCTCCTTCCTCTGTGTCTGCCCCAACAGCCCGGAAGAGTTTGACCCCATGACTGG
ACGCTGTGTTCCCCCACGAACTTCTGCTGACGTGGACGAATGTCAGCTCTTCCGAGACCA
GGTGTGCAAGAGTGGCGTGTGTGTGAACACGGCCCCGGGCTACTCATGCTATTGCAGCAA
CGGCTACTACTACCACACACAGCGGCTGGAGTGCATCGATAATGACGAGTGCGCCGATGA
GGAACCGGCCTGTGAGGGCGGCCGCTGTGTCAACACTGTGGGCTCTTATCACTGTACCTG
CGAGCCCCCACTGGTGCTGGATGGCTCGCAGCGCCGCTGCGTCTCCAACGAGAGCCAGAG
CCTCGATGACAATCTGGGAGTGTGCTGGCAGGAAGTGGGGGCTGACCTCGTGTGCAGCCA
CCCTCGGCTGGACCGTCAGGCCACCTACACAGAGTGCTGCTGCCTGTATGGAGAGGCCTG
GGGCATGGACTGCGCCCTCTGCCCTGCGCAGGACTCAGATGACTTCGAGGCCCTGTGCAA
TGTGCTACGCCCCCCCGCATATAGCCCCCCGCGACCAGGTGGCTTTGGACTCCCCTACGA
GTACGGCCCAGACTTAGGTCCACCTTACCAGGGCCTCCCATATGGGCCTGAGTTGTACCC
ACCACCTGCGCTACCCTACGACCCCTACCCACCGCCACCTGGGCCCTTCGCCCGCCGGGA
GGCTCCTTATGGGGCACCCCGCTTCGACATGCCAGACTTTGAGGACGATGGTGGCCCCTA
TGGCGAATCTGAGGCTCCTGCGCCACCTGGCCCGGGCACCCGCTGGCCCTATCGGTCCCG
GGACACCCGCCGCTCCTTCCCAGAGCCCGAGGAGCCTCCTGAAGGTGGAAGCTATGCTGG
TTCCCTGGCTGAGCCCTACGAGGAGCTGGAGGCCGAGGAGTGCGGGATCCTGGACGGCTG
CACCAACGGCCGCTGCGTGCGCGTCCCCGAAGGCTTCACCTGCCGTTGCTTCGACGGCTA
CCGCCTGGACATGACCCGCATGGCCTGCGTTGACATCAACGAGTGTGATGAGGCCGAGGC
TGCCTCCCCGCTGTGCGTCAACGCGCGTTGCCTCAACACGGATGGCTCCTTCCGCTGCAT
CTGCCGCCCAGGATTTGCACCCACGCACCAGCCACACCACTGTGCGCCCGCACGACCCCG
GGCC**TGA**GCCCTGGCACCCGATGGCCACCCACCCGCGCCCGCCACTCGGGGCCCCTGCCC
CGCATCCTGCAGCCCGCTTAGTCTGATGACGAGGAAGCCCGCCAGAAAGTCCAGAAGAAG
GAACGACGGACGCAAAGCGGCGCCGCCTACCATGCCTCCCCCCCCCACCACCACCCCCCC
CAACTGTGGTCGTCCCCGCCCGGCCCACCCCGCCCCCATTTCTCCCCCCTTCTTTCAATA
AAAATTTCAATCATAAAAAACCACCTATAAAAAAAAAAA

The disclosed NOV6c nucleic acid sequence, which maps to chromosome 19 has 2940 of 3024 bases (97%) identical to a gb:GENBANK-ID:AF051344|acc:AF051344.1 mRNA

from Homo sapiens (Homo sapiens latent transforming growth factor-beta binding protein 4S mRNA, complete cds).

A disclosed NOV6c polypeptide (SEQ ID NO:22) encoded by SEQ ID NO:21 is 1356 amino acid residues and is presented using the one-letter amino acid code in Table 6B. Signal P, Psort and/or Hydropathy results predict that NOV6c contains no signal peptide and is likely to be localized in the cytoplasm with a certainty of 0.6500. In other embodiments, NOV6c is also likely to be localized to the mitochondrial matrix space with a certainty of 0.1000, or the lysosome (lumen) with a certainty of 0.1000.

Table 6F. Encoded NOV6c protein sequence (SEQ ID NO:30).

```
MGRPAPAVPRPARPATPPAWTAALPAGRPRGDPGFRAFLCPLICHNGGVCVKPDRCLCPP
DFAGKFCQLHSSGARPPAPAIPGLTRSVYTMPLANHRDDEHGVASMVSVHVEHPQEASVV
VHQVERVSGPWEEADAEAVARAEAAARAEAAAPYTVLAQSAPREDGYSDASGFGYCFREL
RGGECASPLPGLRTQEVCCRGAGLAWGVHDCQLCSERLGNSERVSAPDGPCPTGFERVNG
SCEDVDECATGGRCQHGECANTRGGYTCVCPDGFLLDSSRSSCISQHVISEAKGPCFRVL
RDGGCSLPILRNITKQICCCSRVGKAWGRGCQLCPPFGSEGFREICPAGPGYHYSASDLR
YNTRPLGQEPPRVSLSQPRTLPATSRPSAGFLPTHRLEPRPEPRPDPRPGPEFPLPSIPA
WTGPEIPESGPSSGMCQRNPQVCGPGRCISRPSGYTCACDSGFRLSPQGTRCIDVDECRR
VPPPCAPGRCENSPGSFRCVCGPGFRAGPRAAECLDVDECHRVPPPCDLGRCENTPGSFL
CVCPAGYQAAPHGASCQDVDECTQSPGLCGRGACKNLPGSFRCVCPAGFRGSACEEDVDE
CAQEPPPCGPGRCDNTAGSFHCACPAGFRSRGPGAPCQDVDECARSPPPCTYGRCENTEG
SFQCVCPMGFQPNAAGSECEDVDECENHLACPGQECVNSPGSFQCRACPSGHHLHRGRCT
DVDECSSGAPPCGPHGHCTNTEGSFRCSCAPGYRAPSGRPGPCADVNECLEGDFCFPHGE
CLNTDGSFACTCAPGYRPGPRGASCLDVDECSEEDLCQSGICTNTDGSFERICPPGHRAG
PDLASCLDVDECRERGPALCGSQRCENSPGSYRCVRDCDPGYHAGPEGTCDDVDECQEYG
PEICGAQRCENTPGSYRCTPACDPGYQPTPGGGCQDVNECETLQGVCGAALCENVEGSFL
CVCPNSPEEFDPMTGRCVPPRTSADVDECQLFRDQVCKSGVCVNTAPGYSCYCSNGYYYH
TQRLECIDNDECADEEPACEGGRCVNTVGSYHCTCEPPLVLDGSQRRCVSNESQSLDDNL
GVCWQEVGADLVCSHPRLDRQATYTECCCLYGEAWGMDCALCPAQDSDDFEALCNVLRPP
AYSPPRPGGFGLPYEYGPDLGPPYQGLPYGPELYPPPALPYDPYPPPPGPFARREAPYGA
PRFDMPDFEDDGGPYGESEAPAPPGPGTRWPYRSRDTRRSFPEPEEPPEGGSYAGSLAEP
YEELEAEECGILDGCTNGRCVRVPEGFTCRCFDGYRLDMTRMACVDINECDEAEAASPLC
VNARCLNTDGSFRCICRPGFAPTHQPHHCAPARPRA
```

The disclosed NOV6c amino acid sequence has 2989 of 3024 bases (98%) identical to a gb:GENBANK-ID:AF051344|acc:AF051344.1 mRNA from Homo sapiens (Homo sapiens latent transforming growth factor-beta binding protein 4S mRNA, complete cds).

NOV6c is expressed in brain. Expression information was derived from the tissue sources of the sequences that were included in the derivation of the sequence of CuraGen Acc. No. CG50215-04. The sequence is predicted to be expressed in the following tissues because of the expression pattern of (GENBANK-ID: gb:GENBANK-ID:AF051344|acc:AF051344.1) a closely related Homo sapiens latent transforming growth factor-beta binding protein 4S mRNA, complete cds homolog in species Homo sapiens :heart, lung, aorta, uterus and small intestine.

NOV6d

A disclosed NOV6d nucleic acid of 4473 nucleotides (also referred to as CG50215-05) encoding a novel TGF-beta binding protein-like protein is shown in Table 6A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 137-139 and ending at a TGA at nucleotides 4199-4201. A putative untranslated region upstream from the initiation codon and downstream from the termination codon is underlined in Table 6A, and the start and stop codons are in bold letters.

Table 6G. NOV6d Nucleotide Sequence (SEQ ID NO:31)

CGGGCGGCGTGCGGCTGCTCTGGGTGTCGCTATTGGTGCTGCTGGCGCAGCTAGGGGCCG
CAGCCTGGACTGGGCCGGCTCGGAGAGCGTCTCCGCGTGCGCTTCACCCCGGTCGTGTGC
GGCCTGCGCTGCGTCC**ATG**GGCCGACCGGCTCCCGCTGTACCCCGACCTGCGCGCCCCGC
AACGCCACCAGCGTGGACAGCGGCGCTCCCGGCGGGGCGGCCCCGGGGGGACCCGGGCTT
CCGCGCCTTCCTGTGTCCCTTGATCTGTCACAATGGCGGTGTGTGCGTGAAGCCTGACCG
CTGCCTCTGTCCCCCGGACTTCGCTGGCAAGTTCTGCCAGTTGCACTCCTCGGGCGCCCG
GCCCCCGGCCCCGGCTATACCAGGCCTCACCCGCTCCGTGTACACTATGCCACTGGCCAA
CCACCGCGACGACGAGCACGGCGTGGCATCTATGGTGAGCGTCCACGTGGAGCACCCGCA
GGAGGCGTCGGTGGTGGTGCACCAGGTGGAGCGTGTGTCTGGCCCTTGGGAGGAGGCGGA
CGCTGAGGCGGTGGCGCGGGCGGAAGCGGCGGCGCGGGCGGAGGCGGCAGCGCCCTACAC
GGTGTTGGCACAGAGCGCGCCGCGGGAGGACGGCTACTCAGATGCCTCGGGCTTCGGTTA
CTGCTTTCGGGAGCTGCGCGGAGGCGAATGCGCGTCCCCGCTGCCCGGGCTCCGGACGCA
GGAGGTCTGCTGCCGAGGGGCCGGCTTGGCCTGGGGCGTTCACGACTGTCAGCTGTGCTC
CGAGCGCCTGGGGAACTCCGAAAGAGTGAGCGCCCCAGATGGACCTTGTCCAACCGGCTT
TGAAAGAGTTAATGGGTCCTGCGAAGATGTGGATGAGTGCGCGACTGGCGGGCGCTGCCA
GCACGGCGAGTGTGCAAACACGCGCGGCGGGTACACGTGTGTGTGCCCCGACGGCTTTCT
GCTCGACTCGTCCCGCAGCAGCTGCATCTCCCAACACGTGATCTCAGAGGCCAAAGGGCC
CTGCTTCCGCGTGCTCCGCGACGGCGGCTGTTCGCTGCCCATTCTGCGGAACATCACTAA
ACAGATCTGCTGCTGCAGCCGCGTAGGCAAGGCCTGGGGCCGGGGCTGCCAGCTCTGCCC
ACCCTTCGGCTCAGAGGGTTTCCGGGAGATCTGCCCGGCTGGTCCTGGTTACCACTACTC
GGCCTCCGACCTCCGCTACAACACCAGACCCCTGGGCCAGGAGCCACCCCGAGTGTCACT
CAGCCAGCCTCGTACCCTGCCAGCCACCTCTCGGCCATCTGCAGGCTTTCTGCCCACCCA
TCGCCTGGAGCCCCGGCCTGAACCCCGGCCCGATCCCCGGCCCGGCCCTGAGTTTCCCTT
GCCCAGCATCCCTGCCTGGACTGGTCCTGAGATTCCTGAATCAGGTCCTTCCTCCGGCAT
GTGTCAGCGCAACCCCCAGGTCTGCGGCCCAGGACGCTGCATTTCCCGGCCCAGCGGCTA
CACCTGCGCTTGCGACTCTGGCTTCCGGCTCAGCCCCCAGGGCACCCGATGCATTGATGT
GGACGAATGTCGCCGCGTGCCCCCGCCCTGTGCTCCCGGGCGCTGCGAGAACTCACCAGG
CAGCTTCCGCTGCGTGTGCGGCCCGGGCTTCCGAGCCGGCCCACGGGCTGCGGAATGCCT
GGATGTGGACGAGTGCCACCGCGTGCCGCCGCCGTGTGACCTCGGGCGCTGCGAGAACAC
GCCAGGCAGCTTCCTGTGCGTGTGCCCCGCCGGGTACCAGGCTGCACCGCACGGAGCCAG
CTGCCAGGATGTGGATGAATGCACCCAGAGCCCAGGCCTGTGTGGCCGAGGGGCCTGCAA
GAACCTGCCTGGCTCTTTCCGCTGTGTTTGCCCGGCTGGCTTCCGGGGCTCGGCGTGTGA
AGAGGATGTGGATGAGTGTGCCCAGGAGCCGCCGCCCTGTGGGCCCGGCCGCTGTGACAA
CACGGCAGGCTCCTTTCACTGTGCCTGCCCTGCTGGCTTCCGCTCCCGAGGGCCCGGGGC
CCCCTGCCAAGATGTGGATGAGTGTGCCCGAAGCCCCCCACCCTGCACCTACGGCCGGTG
TGAGAACACAGAAGGCAGCTTCCAGTGTGTCTGCCCCATGGGCTTCCAACCCAACGCTGC
TGGCTCCGAGTGCGAGGATGTGGATGAGTGTGAGAACCACCTCGCATGCCCTGGGCAGGA
GTGTGTGAACTCGCCCGGCTCCTTCCAGTGCAGGGCCTGTCCTTCTGGCCACCACCTGCA
CCGTGGCAGATGCACTGATGTGGACGAATGCAGTTCGGGTGCCCCTCCCTGTGGTCCCCA
CGGCCACTGCACTAACACCGAAGGCTCCTTCCGCTGCAGCTGCGCGCCAGGCTACCGGGC
GCCGTCGGGTCGGCCCGGGCCCTGCGCAGACGTGAACGAGTGCCTGGAGGGCGATTTCTG
CTTCCCTCACGGCGAGTGCCTCAACACTGACGGCTCCTTTGCCTGTACTTGTGCCCCTGG
CTACCGACCCGGACCCCGCGGAGCCTCTTGCCTCGACGTTGACGAGTGCAGCGAGGAGGA
CCTTTGCCAGAGCGGCATCTGTACCAACACCGACGGCTCCTTCGAGTGCATCTGTCCTCC

GGGACACCGCGCTGGCCCGGACCTCGCCTCCTGCCTCGACGTGGACGAATGTCGCGAGCG
AGGCCCAGCCCTGTGCGGGTCGCAGCGCTGTGAGAACTCTCCCGGCTCCTACCGCTGTGT
CCGGGACTGCGATCCTGGGTACCACGCGGGCCCCGAGGGCACCTGTGACGATGTGGACGA
ATGCCGGAACCGGTCCTTCTGCGGTGCCCACGCCGTGTGCCAGAACCTGCCCGGCTCCTT
CCAGTGCCTCTGTGACCAGGGTTACGAGGGGGCACGGGATGGGCGTCACTGCGTGGATGT
GAACGAGTGTGAAACACTACAGGGTGTATGTGGAGCTGCCCTGTGTGAAAATGTCGAAGG
CTCCTTCCTCTGTGTCTGCCCCAACAGCCCGGAAGAGTTTGACCCCATGACTGGACGCTG
TGTTCCCCCACGAACTTCTGCTGACGTGGACGAATGTCAGCTCTTCCGAGACCAGGTGTG
CAAGAGTGGCGTGTGTGTGAACACGGCCCCGGGCTACTCATGCTATTGCAGCAACGGCTA
CTACTACCACACACAGCGGCTGGAGTGCATCGATAATGACGAGTGCGCCGATGAGGAACC
GGCCTGTGAGGGCGGCCGCTGTGTCAACACTGTGGGCTCTTATCACTGTACCTGCGAGCC
CCCACTGGTGCTGGATGGCTCGCAGCGCCGCTGCGTCTCCAACGAGAGCCAGAGCCTCGA
TGACAATCTGGGAGTGTGCTGGCAGGAAGTGGGGGCTGACCTCGTGTGCAGCCACCCTCG
GCTGGACCGTCAGGCCACCTACACAGAGTGCTGCTGCCTGTATGGAGAGGCCTGGGGCAT
GGACTGCGCCCTCTGCCCTGCGCAGGACTCAGATGACTTCGAGGCCCTGTGCAATGTGCT
ACGCCCCCCCGCATATAGCCCCCCGCGACCAGGTGGCTTTGGACTCCCCTACGAGTACGG
CCCAGACTTAGGTCCACCTTACCAGGGCCTCCCATATGGGCCTGAGTTGTACCCACCACC
TGCGCTACCCTACGACCCCTACCCACCGCCACCTGGGCCCTTCGCCCGCCGGGAGGCTCC
TTATGGGGCACCCCGCTTCGACATGCCAGACTTTGAGGACGATGGTGGCCCCTATGGCGA
ATCTGAGGCTCCTGCGCCACCTGGCCCGGGCACCCGCTGGCCCTATCGGTCCCGGGACAC
CCGCCGCTCCTTCCCAGAGCCCGAGGAGCCTCCTGAAGGTGGAAGCTATGCTGGTTCCCT
GGCTGAGCCCTACGAGGAGCTGGAGGCCGAGGAGTGCGGGATCCTGGACGGCTGCACCAA
CGGCCGCTGCGTGCGCGTCCCCGAAGGCTTCACCTGCCGTTGCTTCGACGGCTACCGCCT
GGACATGACCCGCATGGCCTGCGTTGACATCAACGAGTGTGATGAGGCCGAGGCTGCCTC
CCCGCTGTGCGTCAACGCGCGTTGCCTCAACACGGATGGCTCCTTCCGCTGCATCTGCCG
CCCAGGATTTGCACCCACGCACCAGCCACACCACTGTGCGCCCGCACGACCCCGGGCC**TG**
AGCCCTGGCACCCGATGGCCACCCACCCGCGCCCGCCACTCGGGGCCCCTGCCCCGCATC
CTGCAGCCCGCTTAGTCTGATGACGAGGAAGCCCGCCAGAAAGTCCAGAAGAAGGAACGA
CGGACGCAAAGCGGCGCCGCCTACCATGCCTCCCCCCCCCACCACCACCCCCCCCAACTG
TGGTCGTCCCCGCCCGGCCCACCCCGCCCCCATTTCTCCCCCCTTCTTTCAATAAAAATT
TCAATCATAAAAAACCACCTATAAAAAAAAAAA

The disclosed NOV6d nucleic acid sequence, which maps to chromosome 19 has 2940 of 3024 bases (97%) identical to a gb:GENBANK-ID:AF051344|acc:AF051344.1 mRNA from Homo sapiens (Homo sapiens latent transforming growth factor-beta binding protein 4S mRNA, complete cds).

A disclosed NOV6d polypeptide (SEQ ID NO:22) encoded by SEQ ID NO:21 is 1354 amino acid residues and is presented using the one-letter amino acid code in Table 6B. Signal P, Psort and/or Hydropathy results predict that NOV6d contains no signal peptide and is likely to be localized in the cytoplasm with a certainty of 0.6500. In other embodiments, NOV6d is also likely to be localized to the mitochondrial matrix space with a certainty of 0.1000, or the lysosome (lumen) with a certainty of 0.1000.

Table 6H. Encoded NOV6d protein sequence (SEQ ID NO:32).

MGRPAPAVPRPARPATPPAWTAALPAGRPRGDPGFRAFLCPLICHNGGVCVKPDRCLCPP
DFAGKFCQLHSSGARPPAPAIPGLTRSVYTMPLANHRDDEHGVASMVSVHVEHPQEASVV
VHQVERVSGPWEEADAEAVARAEAAARAEAAAPYTVLAQSAPREDGYSDASGFGYCFREL
RGGECASPLPGLRTQEVCCRGAGLAWGVHDCQLCSERLGNSERVSAPDGPCPTGFERVNG
SCEDVDECATGGRCQHGECANTRGGYTCVCPDGFLLDSSRSSCISQHVISEAKGPCFRVL
RDGGCSLPILRNITKQICCCSRVGKAWGRGCQLCPPFGSEGFREICPAGPGYHYSASDLR
YNTRPLGQEPPRVSLSQPRTLPATSRPSAGFLPTHRLEPRPEPRPDPRPGPEFPLPSIPA

WTGPEIPESGPSSGMCQRNPQVCGPGRCISRPSGYTCACDSGFRLSPQGTRCIDVDECRR
VPPPCAPGRCENSPGSFRCVCGPGFRAGPRAAECLDVDECHRVPPPCDLGRCENTPGSFL
CVCPAGYQAAPHGASCQDVDECTQSPGLCGRGACKNLPGSFRCVCPAGFRGSACEEDVDE
CAQEPPPCGPGRCDNTAGSFHCACPAGFRSRGPGAPCQDVDECARSPPPCTYGRCENTEG
SFQCVCPMGFQPNAAGSECEDVDECENHLACPGQECVNSPGSFQCRACPSGHHLHRGRCT
DVDECSSGAPPCGPHGHCTNTEGSFRCSCAPGYRAPSGRPGPCADVNECLEGDFCFPHGE
CLNTDGSFACTCAPGYRPGPRGASCLDVDECSEEDLCQSGICTNTDGSFECICPPGHRAG
PDLASCLDVDECRERGPALCGSQRCENSPGSYRCVRDCDPGYHAGPEGTCDDVDECRNRS
FCGAHAVCQNLPGSFQCLCDQGYEGARDGRHCVDVNECETLQGVCGAALCENVEGSFLCV
CPNSPEEFDPMTGRCVPPRTSADVDECQLFRDQVCKSGVCVNTAPGYSCYCSNGYYYHTQ
RLECIDNDECADEEPACEGGRCVNTVGSYHCTCEPPLVLDGSQRRCVSNESQSLDDNLGV
CWQEVGADLVCSHPRLDRQATYTECCCLYGEAWGMDCALCPAQDSDDFEALCNVLRPPAY
SPPRPGGFGLPYEYGPDLGPPYQGLPYGPELYPPPALPYDPYPPPPGPFARREAPYGAPR
FDMPDFEDDGGPYGESEAPAPPGPGTRWPYRSRDTRRSFPEPEEPPEGGSYAGSLAEPYE
ELEAEECGILDGCTNGRCVRVPEGFTCRCFDGYRLDMTRMACVDINECDEAEAASPLCVN
ARCLNTDGSFRCICRPGFAPTHQPHHCAPARPRA

The disclosed NOV6d amino acid sequence has 2940 of 3024 bases (97%) identical to a gb:GENBANK-ID:AF051344|acc:AF051344.1 mRNA from Homo sapiens (Homo sapiens latent transforming growth factor-beta binding protein 4S mRNA, complete cds).

NOV6d is expressed in Adrenal gland, bone marrow, brain, kidney, liver, lung, heart, mammary gland, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thyroid, trachea, uterus, bone, cervix, and ovary. Expression information was derived from the tissue sources of the sequences that were included in the derivation of the sequence of CuraGen Acc. No. CG50215-05. The sequence is predicted to be expressed in the following tissues because of the expression pattern of (GENBANK-ID: gb:GENBANK-ID:AF051344|acc:AF051344.1) a closely related Homo sapiens latent transforming growth factor-beta binding protein 4S mRNA: heart.

NOV6 also has homology to the amino acid sequences shown in the BLASTP data listed in Table 6I.

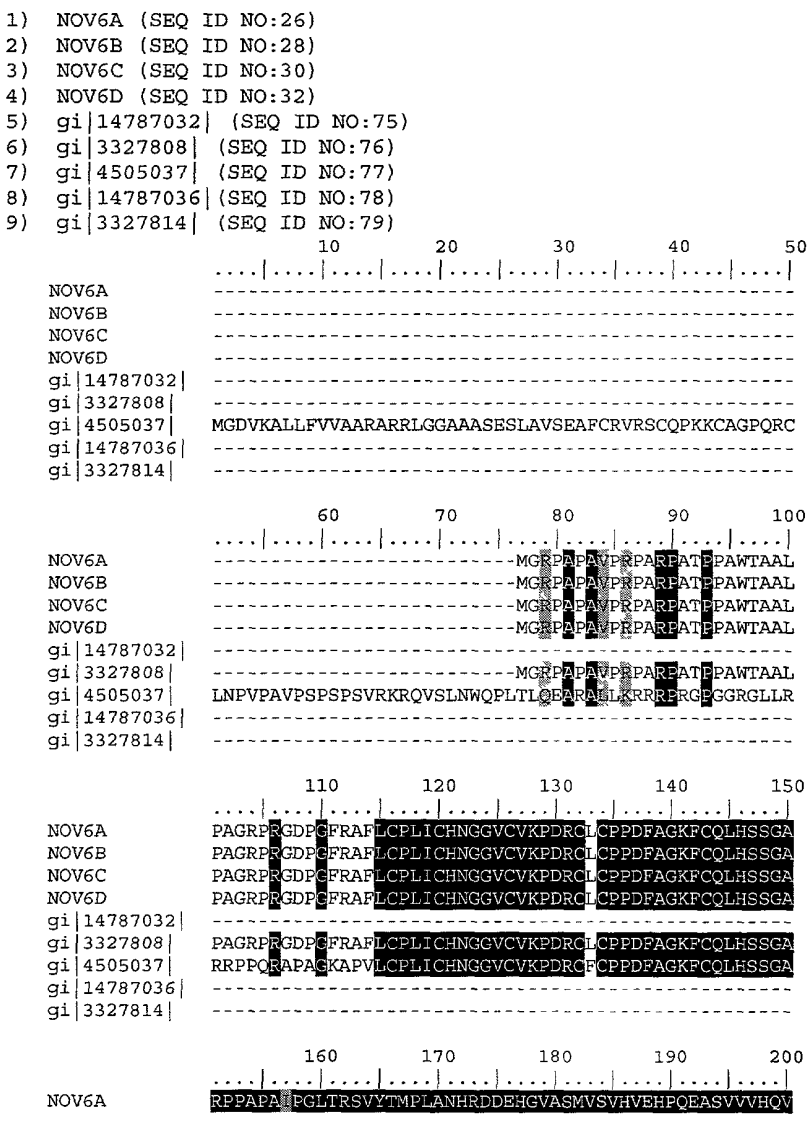
Table 6I. BLAST results for NOV6

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|3327808 gb AAC39 879.1 (AF051344)	latent transforming growth factor-beta binding protein 4S [Homo sapiens]	1511	97	97	0.0
gi|4505037 ref|NP_0 03564.1| (NM_003573)	latent transforming growth factor beta binding protein 4 [Homo sapiens]	1587	92	92	0.0

gi|14787032 ref XP 047374.1 (XM_047374)	latent transforming growth factor beta binding protein 4 [Homo sapiens]	888	97	97	0.0
gi|3327814 gb AAC39882.1 (AF054502)	latent transforming growth factor-beta binding protein 4 [Homo sapiens]	669	91	91	0.0
gi|14787036 ref XP 008868.4 (XM_008868)	hypothetical protein XP_008868 [Homo sapiens]	775	99	99	0.0

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 6J.

Table 6J Information for the ClustalW proteins



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NOV6B            RPPAPAIPGLTRSVYTMPLANHRDDEHGVASMVSVHVEHPQEASVVVHQV
NOV6C            RPPAPAIPGLTRSVYTMPLANHRDDEHGVASMVSVHVEHPQEASVVVHQV
NOV6D            RPPAPAIPGLTRSVYTMPLANHRDDEHGVASMVSVHVEHPQEASVVVHQV
gi|14787032|     ----------------MPLANHRDDEHGVASMVSVHVEHPQEASVVVHQV
gi|3327808|      RPPAPAIPGLTRSVYTMPLANHRDDEHGVASMVSVHVEHPQEASVVVHQV
gi|4505037|      RPPAPAVPGLTRSVYTMPLANHRDDEHGVASMVSVHVEHPQEASVVVHQV
gi|14787036|     ----------------MPLANHRDDEHGVASMVSVHVEHPQEASVVVHQV
gi|3327814|      --------------------------------------------------

                         210       220       230       240       250
                 ....|....|....|....|....|....|....|....|....|....|
NOV6A            ERVSGPWEEADAEAVARAEAAARAEAAAPYTVLAQSAPREDGYSDASGFG
NOV6B            ERVSGPWEEADAEAVARAEAAARAEAAAPYTVLAQSAPREDGYSDASGFG
NOV6C            ERVSGPWEEADAEAVARAEAAARAEAAAPYTVLAQSAPREDGYSDASGFG
NOV6D            ERVSGPWEEADAEAVARAEAAARAEAAAPYTVLAQSAPREDGYSDASGFG
gi|14787032|     ERVSGPWEEADAEAVARAEAAARAEAAAPYTVLAQSAPREDGYSDASGFG
gi|3327808|      ERVSGPWEEADAEAVARAEAAARAEAAAPYTVLAQSAPREDGYSDASGFG
gi|4505037|      ERVSGPWEEADAEAVARAEAAARAEAAAPYTVLAQSAPREDGYSDASGFG
gi|14787036|     ERVSGPWEEADAEAVARAEAAARAEAAAPYTVLAQSAPREDGYSDASGFG
gi|3327814|      --------------------------------------------------

                         260       270       280       290       300
                 ....|....|....|....|....|....|....|....|....|....|
NOV6A            YCFRELRGGECASPLPGLRTQEVCCRGAGLAWGVHDCQLCSERLGNSERV
NOV6B            YCFRELRGGECASPLPGLRTQEVCCRGAGLAWGVHDCQLCSERLGNSERV
NOV6C            YCFRELRGGECASPLPGLRTQEVCCRGAGLAWGVHDCQLCSERLGNSERV
NOV6D            YCFRELRGGECASPLPGLRTQEVCCRGAGLAWGVHDCQLCSERLGNSERV
gi|14787032|     YCFRELRGGECASPLPGLRTQEVCCRGAGLAWGVHDCQLCSERLGNSERV
gi|3327808|      YCFRELRGGECASPLPGLRTQEVCCRGAGLAWGVHDCQLCSERLGNSERV
gi|4505037|      YCFRELRGGECASPLPGLRTQEVCCRGAGLAWGVHDCQLCSERLGNSERV
gi|14787036|     YCFRELRGGECASPLPGLRTQEVCCRGAGLAWGVHDCQLCSERLGNSERV
gi|3327814|      --------------------------------------------------

                         310       320       330       340       350
                 ....|....|....|....|....|....|....|....|....|....|
NOV6A            SAPDGPCPTGFERVNGSCEDVDECATGGRCQHGECANTRGGYTCVCPDGF
NOV6B            SAPDGPCPTGFERVNGSCEDVDECATGGRCQHGECANTRGGYTCVCPDGF
NOV6C            SAPDGPCPTGFERVNGSCEDVDECATGGRCQHGECANTRGGYTCVCPDGF
NOV6D            SAPDGPCPTGFERVNGSCEDVDECATGGRCQHGECANTRGGYTCVCPDGF
gi|14787032|     SAPDGPCPTGFERVNGSCEDVDECATGGRCQHGECANTRGGYTCVCPDGF
gi|3327808|      SAPDGPCPTGFERVNGSCEDVDECATGGRCQHGECANTRGGYTCVCPDGF
gi|4505037|      SAPDGPCPTGFERVNGSCEDVDECATGGRCQHGECANTRGGYTCVCPDGF
gi|14787036|     SAPDGPCPTGFERVNGSCEDVDECATGGRCQHGECANTRGGYTCVCPDGF
gi|3327814|      --------------------------------------------------

                         360       370       380       390       400
                 ....|....|....|....|....|....|....|....|....|....|
NOV6A            LLDSSRSSCISQHVISEAKGPCFRVLRDGGCSLPILRNITKQICCCSRVG
NOV6B            LLDSSRSSCISQHVISEAKGPCFRVLRDGGCSLPILRNITKQICCCSRVG
NOV6C            LLDSSRSSCISQHVISEAKGPCFRVLRDGGCSLPILRNITKQICCCSRVG
NOV6D            LLDSSRSSCISQHVISEAKGPCFRVLRDGGCSLPILRNITKQICCCSRVG
gi|14787032|     LLDSSRSSCISQHVISEAKGPCFRVLRDGGCSLPILRNITKQICCCSRVG
gi|3327808|      LLDSSRSSCISQHVISEAKGPCFRVLRDGGCSLPILRNITKQICCCSRVG
gi|4505037|      LLDSSRSSCISQHVISEAKGPCFRVLRDGGCSLPILRNITKQICCCSRVG
gi|14787036|     LLDSSRSSCISQHVISEAKGPCFRVLRDGGCSLPILRNITKQICCCSRVG
gi|3327814|      --------------------------------------------------

                         410       420       430       440       450
                 ....|....|....|....|....|....|....|....|....|....|
NOV6A            KAWGRGCQLCPPFGSEGFREICPAGPGYHYSASDLRYNTRPLGQEPPRVS
NOV6B            KAWGRGCQLCPPFGSEGFREICPAGPGYHYSASDLRYNTRPLGQEPPRVS
NOV6C            KAWGRGCQLCPPFGSEGFREICPAGPGYHYSASDLRYNTRPLGQEPPRVS
NOV6D            KAWGRGCQLCPPFGSEGFREICPAGPGYHYSASDLRYNTRPLGQEPPRVS
gi|14787032|     KAWGRGCQLCPPFGSEGFREICPAGPGYHYSASDLRYNTRPLGQEPPRVS
gi|3327808|      KAWGRGCQLCPPFGSEGFREICPAGPGYHYSASDLRYNTRPLGQEPPRVS
gi|4505037|      KAWGRGCQLCPPFGSEGFREICPAGPGYHYSASDLRYNTRPLGQEPPRVS
gi|14787036|     KAWGRGCQLCPPFGSEGFREICPAGPGYHYSASDLRYNTRPLGQEPPRVS
gi|3327814|      --------------------------------------------------

                         460       470       480       490       500
                 ....|....|....|....|....|....|....|....|....|....|
NOV6A            LSQPRTLPATSRPSAGFLPTHRLEPRPEPRPDPRPGPEFPLPSIPAWTGP
NOV6B            LSQPRTLPATSRPSAGFLPTHRLEPRPEPRPDPRPGPEFPLPSIPAWTGP
NOV6C            LSQPRTLPATSRPSAGFLPTHRLEPRPEPRPDPRPGPEFPLPSIPAWTGP
NOV6D            LSQPRTLPATSRPSAGFLPTHRLEPRPEPRPDPRPGPEFPLPSIPAWTGP
gi|14787032|     LSQPRTLPATSRPSAGFLPTHRLEPRPEPRPDPRPGPELPLPSIPAWTGP
gi|3327808|      LSQPRTLPATSRPSAGFLPTHRLEPRPEPRPDPRPGPEFPLPSIPAWTGP
gi|4505037|      LSQPRTLPATSRPSAGFLPTHRLEPRPEPRPDPRPGPELPLPSIPAWTGP
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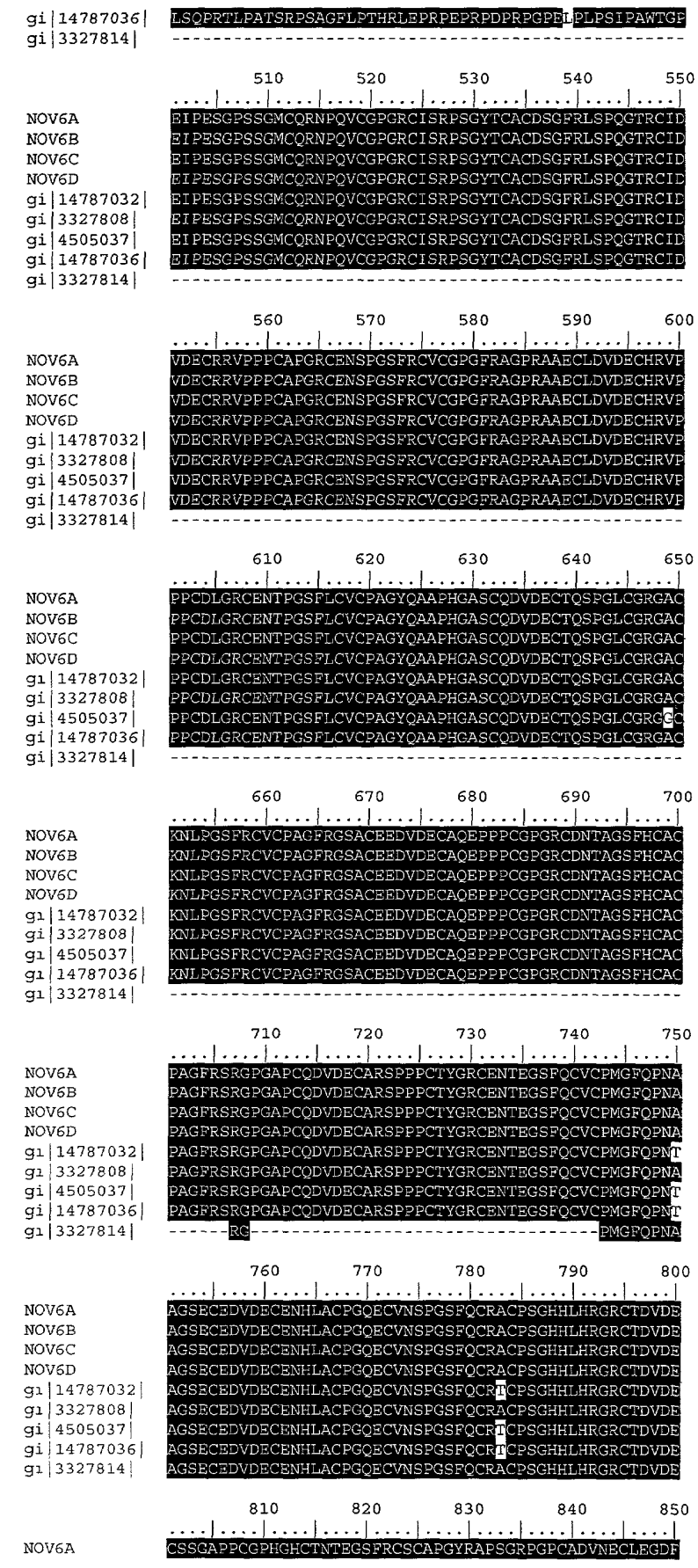
gi|14787036| LSQPRTLPATSRPSAGFLPTHRLEPRPEPRPDPRPGPELPLPSIPAWTGP
gi|3327814| ----------
510 520 530 540 550
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NOV6B EIPESGPSSGMCQRNPQVCGPGRCISRPSGYTCACDSGFRLSPQGTRCID
NOV6C EIPESGPSSGMCQRNPQVCGPGRCISRPSGYTCACDSGFRLSPQGTRCID
NOV6D EIPESGPSSGMCQRNPQVCGPGRCISRPSGYTCACDSGFRLSPQGTRCID
gi|14787032| EIPESGPSSGMCQRNPQVCGPGRCISRPSGYTCACDSGFRLSPQGTRCID
gi|3327808| EIPESGPSSGMCQRNPQVCGPGRCISRPSGYTCACDSGFRLSPQGTRCID
gi|4505037| EIPESGPSSGMCQRNPQVCGPGRCISRPSGYTCACDSGFRLSPQGTRCID
gi|14787036| EIPESGPSSGMCQRNPQVCGPGRCISRPSGYTCACDSGFRLSPQGTRCID
gi|3327814| ----------
560 570 580 590 600
NOV6A VDECRRVPPPCAPGRCENSPGSFRCVCGPGFRAGPRAAECLDVDECHRVP
NOV6B VDECRRVPPPCAPGRCENSPGSFRCVCGPGFRAGPRAAECLDVDECHRVP
NOV6C VDECRRVPPPCAPGRCENSPGSFRCVCGPGFRAGPRAAECLDVDECHRVP
NOV6D VDECRRVPPPCAPGRCENSPGSFRCVCGPGFRAGPRAAECLDVDECHRVP
gi|14787032| VDECRRVPPPCAPGRCENSPGSFRCVCGPGFRAGPRAAECLDVDECHRVP
gi|3327808| VDECRRVPPPCAPGRCENSPGSFRCVCGPGFRAGPRAAECLDVDECHRVP
gi|4505037| VDECRRVPPPCAPGRCENSPGSFRCVCGPGFRAGPRAAECLDVDECHRVP
gi|14787036| VDECRRVPPPCAPGRCENSPGSFRCVCGPGFRAGPRAAECLDVDECHRVP
gi|3327814| ----------
610 620 630 640 650
NOV6A PPCDLGRCENTPGSFLCVCPAGYQAAPHGASCQDVDECTQSPGLCGRGAC
NOV6B PPCDLGRCENTPGSFLCVCPAGYQAAPHGASCQDVDECTQSPGLCGRGAC
NOV6C PPCDLGRCENTPGSFLCVCPAGYQAAPHGASCQDVDECTQSPGLCGRGAC
NOV6D PPCDLGRCENTPGSFLCVCPAGYQAAPHGASCQDVDECTQSPGLCGRGAC
gi|14787032| PPCDLGRCENTPGSFLCVCPAGYQAAPHGASCQDVDECTQSPGLCGRGAC
gi|3327808| PPCDLGRCENTPGSFLCVCPAGYQAAPHGASCQDVDECTQSPGLCGRGAC
gi|4505037| PPCDLGRCENTPGSFLCVCPAGYQAAPHGASCQDVDECTQSPGLCGRGSC
gi|14787036| PPCDLGRCENTPGSFLCVCPAGYQAAPHGASCQDVDECTQSPGLCGRGAC
gi|3327814| ----------
660 670 680 690 700
NOV6A KNLPGSFRCVCPAGFRGSACEEDVDECAQEPPPCGPGRCDNTAGSFHCAC
NOV6B KNLPGSFRCVCPAGFRGSACEEDVDECAQEPPPCGPGRCDNTAGSFHCAC
NOV6C KNLPGSFRCVCPAGFRGSACEEDVDECAQEPPPCGPGRCDNTAGSFHCAC
NOV6D KNLPGSFRCVCPAGFRGSACEEDVDECAQEPPPCGPGRCDNTAGSFHCAC
gi|14787032| KNLPGSFRCVCPAGFRGSACEEDVDECAQEPPPCGPGRCDNTAGSFHCAC
gi|3327808| KNLPGSFRCVCPAGFRGSACEEDVDECAQEPPPCGPGRCDNTAGSFHCAC
gi|4505037| KNLPGSFRCVCPAGFRGSACEEDVDECAQEPPPCGPGRCDNTAGSFHCAC
gi|14787036| KNLPGSFRCVCPAGFRGSACEEDVDECAQEPPPCGPGRCDNTAGSFHCAC
gi|3327814| ----------
710 720 730 740 750
NOV6A PAGFRSRGPGAPCQDVDECARSPPPCTYGRCENTEGSFQCVCPMGFQPNA
NOV6B PAGFRSRGPGAPCQDVDECARSPPPCTYGRCENTEGSFQCVCPMGFQPNA
NOV6C PAGFRSRGPGAPCQDVDECARSPPPCTYGRCENTEGSFQCVCPMGFQPNA
NOV6D PAGFRSRGPGAPCQDVDECARSPPPCTYGRCENTEGSFQCVCPMGFQPNA
gi|14787032| PAGFRSRGPGAPCQDVDECARSPPPCTYGRCENTEGSFQCVCPMGFQPNT
gi|3327808| PAGFRSRGPGAPCQDVDECARSPPPCTYGRCENTEGSFQCVCPMGFQPNA
gi|4505037| PAGFRSRGPGAPCQDVDECARSPPPCTYGRCENTEGSFQCVCPMGFQPNT
gi|14787036| PAGFRSRGPGAPCQDVDECARSPPPCTYGRCENTEGSFQCVCPMGFQPNT
gi|3327814| ------RG----------PMGFQPNA
760 770 780 790 800
NOV6A AGSECEDVDECENHLACPGQECVNSPGSFQCRACPSGHHLHRGRCTDVDE
NOV6B AGSECEDVDECENHLACPGQECVNSPGSFQCRACPSGHHLHRGRCTDVDE
NOV6C AGSECEDVDECENHLACPGQECVNSPGSFQCRACPSGHHLHRGRCTDVDE
NOV6D AGSECEDVDECENHLACPGQECVNSPGSFQCRACPSGHHLHRGRCTDVDE
gi|14787032| AGSECEDVDECENHLACPGQECVNSPGSFQCRTCPSGHHLHRGRCTDVDE
gi|3327808| AGSECEDVDECENHLACPGQECVNSPGSFQCRACPSGHHLHRGRCTDVDE
gi|4505037| AGSECEDVDECENHLACPGQECVNSPGSFQCRTCPSGHHLHRGRCTDVDE
gi|14787036| AGSECEDVDECENHLACPGQECVNSPGSFQCRTCPSGHHLHRGRCTDVDE
gi|3327814| AGSECEDVDECENHLACPGQECVNSPGSFQCRACPSGHHLHRGRCTDVDE
810 820 830 840 850
NOV6A CSSGAPPCGPHGHCTNTEGSFRCSCAPGYRAPSGRPGPCADVNECLEGDF

```
NOV6B          CSSGAPPCGPHGHCTNTEGSFRCSCAPGYRAPSGRPGPCADVNECLEGDF
NOV6C          CSSGAPPCGPHGHCTNTEGSFRCSCAPGYRAPSGRPGPCADVNECLEGDF
NOV6D          CSSGAPPCGPHGHCTNTEGSFRCSCAPGYRAPSGRPGPCADVNECLEGDF
gi|14787032|   CSSGAPPCGPHGHCTNTEGSFRCSCAPGYRAPSGRPGPCADVNECLEGDF
gi|3327808|    CSSGAPPCGPHGHCTNTEGSFRCSCAPGYRAPSGRPGPCADVNECLEGDF
gi|4505037|    CSSGAPPCGPHGHCTNTEGSFRCSCAPGYRAPSGRPGPCADVNECLEGDF
gi|14787036|   CSSGAPPCGPHGHCTNTEGSFRCSCAPGYRAPSGRPGPCADVNECLEGDF
gi|3327814|    CSSGAPPCGPHGHCTNTEGSFRCSCAPGYRAPSGRPGPCADVNECLEGDF

                        860       870       880       890       900
               ....|....|....|....|....|....|....|....|....|....|
NOV6A          CFPHGECLNTDGSFACTCAPGYRPGPRGASCLDVDECSEEDLCQSGICTN
NOV6B          CFPHGECLNTDGSFACTCAPGYRPGPRGASCLDVDECSEEDLCQSGICTN
NOV6C          CFPHGECLNTDGSFACTCAPGYRPGPRGASCLDVDECSEEDLCQSGICTN
NOV6D          CFPHGECLNTDGSFACTCAPGYRPGPRGASCLDVDECSEEDLCQSGICTN
gi|14787032|   CFPHGECLNTDGSFACTCAPGYRPGPRGASCLDVDECSEEDLCQSGICTN
gi|3327808|    CFPHGECLNTDGSFACTCAPGYRPGPRGASCLDVDECSEEDLCQSGICTN
gi|4505037|    CFPHGECLNTDGSFACTCAPGYRPGPRGASCLDVDECSEEDLCQSGICTN
gi|14787036|   CFPHGECLNTDGSFACTCAPGYRPGPRGASCLDVDECSEEDLCQSGICTN
gi|3327814|    CFPHGECLNTDGSFACTCAPGYRPGPRGASCLDVDECSEEDLCQSGICTN

                        910       920       930       940       950
               ....|....|....|....|....|....|....|....|....|....|
NOV6A          TDGSFERICPPGHRAGPDLASCLDVDECRERGPALCGSQRCENSPGSYRC
NOV6B          TDGSFECICPPGHRAGPDLASCLDVDECRERGPALCGSQRCENSPGSYRC
NOV6C          TDGSFERICPPGHRAGPDLASCLDVDECRERGPALCGSQRCENSPGSYRC
NOV6D          TDGSFECICPPGHRAGPDLASCLDVDECRERGPALCGSQRCENSPGSYRC
gi|14787032|   TDGSFECICPPGHRAGPDLASCLDVDECRERGPALCGSQRCENSPGSYRC
gi|3327808|    TDGSFECICPPGHRAGPDLASCLDVDECRERGPALCGSQRCENSPGSYRC
gi|4505037|    TDGSFECICPPGHRAGPDLASCLDVDECRERGPALCGSQRCENSPGSYRC
gi|14787036|   TDGSFECICPPGHRAGPDLASCLG------RG----RMSRARPSP-----
gi|3327814|    TDGSFECICPPGHRAGPDLASCLDVDECRERGPALCGSQRCENSPGSYRC

                        960       970       980       990      1000
               ....|....|....|....|....|....|....|....|....|....|
NOV6A          VRDCDPGYHAGPEGTCDDVDECQEYGPEICGAQR-CENTPGSYRCTPACD
NOV6B          VRDCDPGYHAGPEGTCDDVDECRNR--SFCGAHAVCQNLPGSFQC--LCD
NOV6C          VRDCDPGYHAGPEGTCDDVDECQEYGPEICGAQR-CENTPGSYRCTPACD
NOV6D          VRDCDPGYHAGPEGTCDDVDECRNR--SFCGAHAVCQNLPGSFQC--LCD
gi|14787032|   VRDCDPGYHAGPEGTCDDVDECQEYGPEICGAQR-CENTPGSYRCTPACD
gi|3327808|    VRDCDPGYHAGPEGTCDDVDECQEYGPEICGAQR-CENTPGSYRCTPACD
gi|4505037|    VRDCDPGYHAGPEGTCDDVDECQEYGPEICGAQR-CENTPGSYRCTPACD
gi|14787036|   VRVAAL--------------------------------------------
gi|3327814|    VRDCDPGYHAGPEGTCDDVNECETLQ-GVCGAAL-CENVEGSFLCVCPNS

                       1010      1020      1030      1040      1050
               ....|....|....|....|....|....|....|....|....|....|
NOV6A          PGYQ-PTPGGGCQDVNECETLQGVCGAALCENVEGSFLCVCPNSPEEFDP
NOV6B          QGYEGARDGRHCVDVNECETLQGVCGAALCENVEGSFLCVCPNSPEEFDP
NOV6C          PGYQ-PTPGGGCQDVNECETLQGVCGAALCENVEGSFLCVCPNSPEEFDP
NOV6D          QGYEGARDGRHCVDVNECETLQGVCGAALCENVEGSFLCVCPNSPEEFDP
gi|14787032|   PGYQ-PTPGGGCQDVDECRNRSFCGAHAVCQNLPGSFQCLCDQVTRGHGM
gi|3327808|    PGYQ-PTPGGGCQDVDECRNRSFCGAHAVCQNLPGSFQCLCDQGYEGARD
gi|4505037|    PGYQ-PTPGGGCQDVDECRNRSFCGAHAVCQNLPGSFQCLCDQGYEGARD
gi|14787036|   --------------------------------------------------
gi|3327814|    PEEFDPMTGRCVPPRTSAGMFPGSQPQAPASPVLPARPPPPPLPRRPSTP

                       1060      1070      1080      1090      1100
               ....|....|....|....|....|....|....|....|....|....|
NOV6A          MTGRCVP------------------------------------------P
NOV6B          MTGRCVP------------------------------------------P
NOV6C          MTGRCVP-------------------------------------------
NOV6D          MTGRCVP-------------------------------------------
gi|14787032|   GVTAWM--------------------------------------------
gi|3327808|    GRHCVDVNECETLQGVCGAALCENVEGSFLCVCPNSPEEFDPMTGRCVPP
gi|4505037|    GRHCVDVNECETLQGVCGAALCENVEGSFLCVCPNSPEEFDPMTGRCVPP
gi|14787036|   --------------------------------------------------
gi|3327814|    RQGPVGS-------------------------------------------

                       1110      1120      1130      1140      1150
               ....|....|....|....|....|....|....|....|....|....|
NOV6A          RTSAGTFPGSQPQAPASPVLPARPPPPPLPRRPSTPRQGPVGSGRRECYF
NOV6B          RTSAGTFPGSQPQAPASPVLPARPPPPPLPRRPSTPRQGPVGSGRRECYF
NOV6C          --------------------------------------------------
NOV6D          --------------------------------------------------
gi|14787032|   --------------------------------------------------
gi|3327808|    RTSAGMFPGSQPQAPASPVLPARPPPPPLPRRPSTPRQGPVGSGRRECYF
gi|4505037|    RTSVGMSPGSQPQAPVSPVLPARPPPPPLSRRPRKPRKGPVGSGCRECYF
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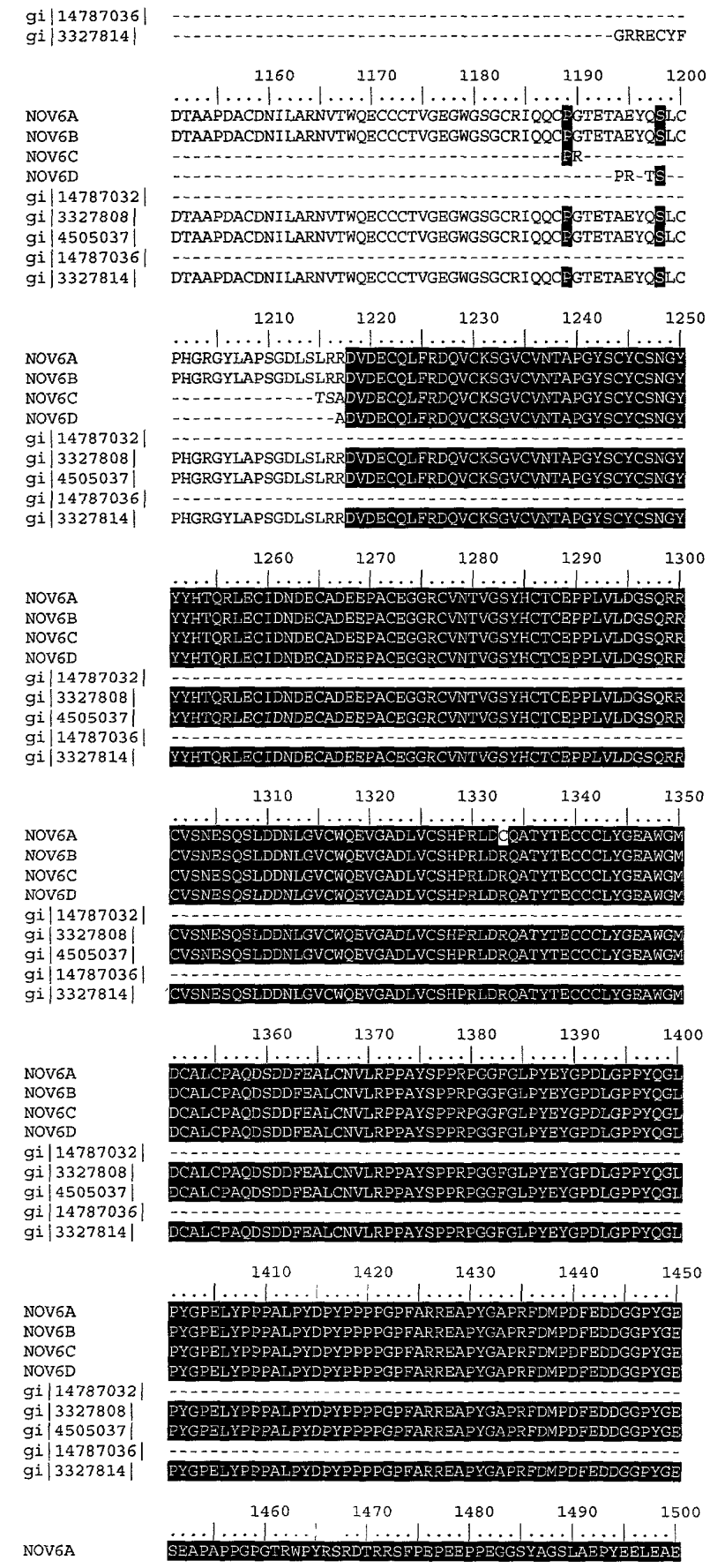
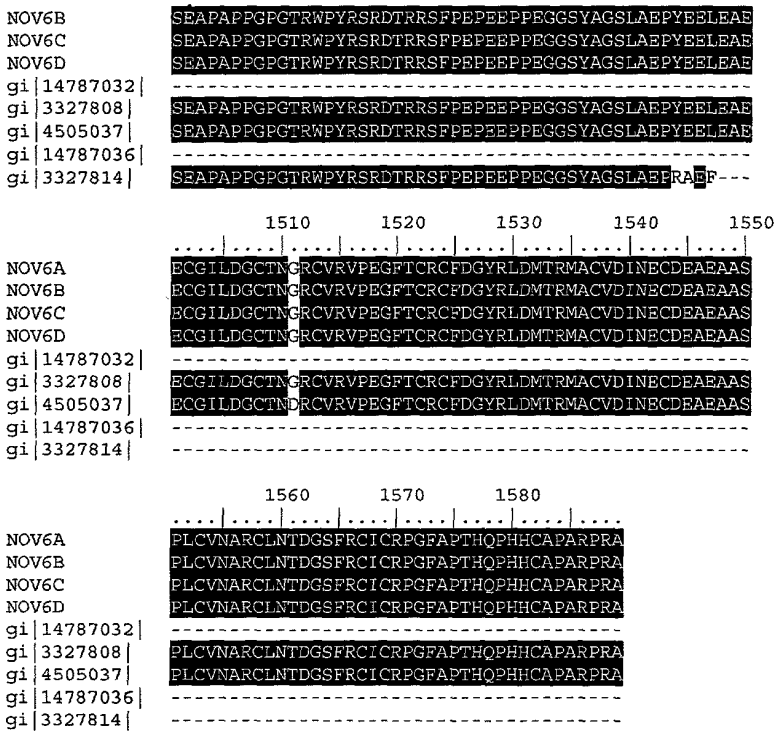




In human tissues, normal homeostasis requires intricately balanced interactions between cells and the network of secreted proteins known as the extracellular matrix. These cooperative interactions involve numerous cytokines acting through specific cell-surface receptors. When the balance between the cells and the extracellular matrix is perturbed, disease can result. This is clearly evident in the interactions mediated by the cytokine transforming growth factor (beta) (TGF-(beta)).

TGF-(beta) is a member of a family of dimeric polypeptide growth factors that includes bone morphogenic proteins and activins. All of these growth factors share a cluster of conserved cysteine residues that form a common cysteine knot structure held together by intramolecular disulfide bonds. Virtually every cell in the body, including epithelial, endothelial, hematopoietic, neuronal, and connective-tissue cells, produces TGF-(beta) and has receptors for it. TGF-(beta) regulates the proliferation and differentiation of cells, embryonic development, wound healing, and angiogenesis. The essential role of the TGF-(beta) signaling pathway in these processes has been demonstrated by targeted deletion of the genes encoding members of this pathway in mice.

The biological activity of the transforming growth factor-beta's (TGF-beta) is tightly controlled by their persistance in the extracellular compartment as latent complexes. Each of the three mammalian isoform genes encodes a product that is cleaved intracellularly to form two polypeptides, each of which dimerizes. Mature TGF-beta, a 24 kD homodimer, is

noncovalently associated with the 80 kD latency-associated peptide (LAP). LAP is a fundamental component of TGF-beta that is required for its efficient secretion, prevents it from binding to ubiquitous cell surface receptors, and maintains its availability in a large extracellular reservoir that is readily accessed by activation. This latent TGF-beta complex (LTGF-beta) is secreted by all cells and is abundant both in circulating forms and bound to the extracellular matrix. Activation describes the collective events leading to the release of TGF-beta. Despite the importance of TGF-beta regulation of growth and differentiation in physiological and malignant tissue processes, remarkably little is known about the mechanisms of activation in situ. Recent studies of irradiated mammary gland reveal certain features of TGF-beta 1 activation that may shed light on its regulation and potential roles in the normal and neoplastic mammary gland.

Transforming growth factor (TGF)-betas are secreted in large latent complexes consisting of TGF-beta, its N-terminal latency-associated peptide (LAP) propeptide, and latent TGF-beta binding protein (LTBP). LTBPs are required for secretion and subsequent deposition of TGF-beta into the extracellular matrix. TGF-beta1 associates with the 3(rd) 8-Cys repeat of LTBP-1 by LAP. All LTBPs, as well as fibrillins, contain multiple 8-Cys repeats. 8-Cys repeat has been found to interact with TGF-beta1*LAP by direct cysteine bridging. LTBP-1 and LTBP-3 bind efficiently all TGF-beta isoforms, LTBP-4 has a much weaker binding capacity, whereas LTBP-2 as well as fibrillins -1 and -2 are negative. A short, specific TGF-beta binding motif has been identified in the TGF-beta binding 8-Cys repeats. Deletion of this motif in the 3(rd) 8-Cys repeat of LTBP-1 results in loss of TGF-beta*LAP binding ability, while its inclusion in non-TGF-beta binding 3(rd) 8-Cys repeat of LTBP-2 results in TGF-beta binding. Molecular modeling of the 8-Cys repeats has revealed a hydrophobic interaction surface and lack of three stabilizing hydrogen bonds introduced by the TGF-beta binding motif necessary for the formation of the TGF-beta*LAP - 8-Cys repeat complex inside the cells.

LTBP-4 gene has been localized to chromosomal position 19q13. 1-19q13.2. The major LTBP-4 mRNA form is about 5.1 kilobase pairs in size and is predominantly expressed in the heart, aorta, uterus, and small intestine. Immunoblotting analysis has indicated that LTBP-4 was secreted from cultured human lung fibroblasts both in a free form and in a disulfide bound complex with a TGF-beta. LAP-like protein. The matrix-associated LTBP-4 was susceptible to proteolytic release with plasmin. LTBP-4 is a member of the growing LTBP-fibrillin family of proteins and offers an alternative means for the secretion and targeted matrix deposition of TGF-betas or related proteins.

LTBP-4 consists of 20 EG modules, 17 of them with a consensus sequence for calcium binding, 4 TB modules with 8 cysteines and several proline-rich regions. Northern blots demonstrated a single 5 kb mRNA which is highly expressed in heart but also present in skeletal muscle, pancreas, placenta and lung. The modular structure predicts that LTBP-4 should be a microfibrillar protein which probably also binds TGF-beta.

Increases or decreases in the production of TGF-(beta) have been linked to several disease states, including atherosclerosis and fibrotic disease of the kidney, liver, and lung, as well as in development. Mice lacking TGF-(beta)2 have cardiac, lung, craniofacial, and urogenital defects, and mice lacking TGF-(beta)3 have cleft palates. Polymorphisms in the gene for TGF-(beta)3 have been linked to the development of cleft palate in humans. Mutations in the genes for TGF-(beta), its receptors, or intracellular signaling molecules associated with TGF-(beta) are also important in the pathogenesis of diseases, particularly cancer and hereditary hemorrhagic telangiectasia.

The disclosed NOV6 nucleic acid of the invention encoding a TGF-beta binding protein-like protein includes the nucleic acid whose sequence is provided in Table 6A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 6A while still encoding a protein that maintains its TGF-beta binding protein-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 3 percent of the bases may be so changed.

The disclosed NOV6 protein of the invention includes the TGF-beta binding protein-like protein whose sequence is provided in Table 6B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 6B while still encoding a protein that maintains its TGF-beta binding protein-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 15 percent of the residues may be so changed.

The above defined information for this invention suggests that these TGF-beta binding protein-like proteins (NOV6) may function as a member of a "TGF-beta binding protein family". Therefore, the NOV6 nucleic acids and proteins identified here may be useful in potential therapeutic applications implicated in (but not limited to) various pathologies and disorders as indicated below. The potential therapeutic applications for this invention include, but are not limited to: protein therapeutic, small molecule drug target, antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), diagnostic and/or prognostic marker, gene therapy (gene delivery/gene ablation), research tools, tissue regeneration *in vivo* and *in vitro* of all tissues and cell types composing (but not limited to) those defined here.

The nucleic acids and proteins of NOV6 are useful in from atherosclerosis and fibrotic disease of the kidney, liver, and lung, and cancer (e.g. cancer of epithelial, endothelial, and hematopoietic cells), hereditary hemorrhagic telangiectasia., and/or other pathologies and disorders. The novel NOV6 nucleic acid encoding NOV6 protein,, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods.

NOV6 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV6a protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV6 epitope is from about amino acids 1 to 50. In other embodiments, NOV6 epitope is from about amino acids 220 to 300, from about amino acids 900 to 950, or from about amino acids 1150 to 1200. This novel protein also has value in development of powerful assay system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV7

A disclosed NOV7 nucleic acid of 973 nucleotides (also referred to as GMAP00808_A_da1) encoding a novel MAS proto-oncogene-like protein is shown in Table 7A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 3-5 and ending with a TGA codon at nucleotides 966-968.

Table 7A. NOV7 Nucleotide Sequence (SEQ ID NO:33)

```
GGATGAACCAGACTTTGAATAGCAGTGGGACCGTGGAGTCAGCCCTAAACTATTCCAGAGGGAGCACAGT
GCACACGGCCTACCTGGTGCTGAGCTCCCTGGCCATGTTCACCTGCCTGTGCGGGATGGCAGGCAACAGC
ATGGTGATCTGGCTGCTAGGCTTTCGAATGCACAGGAACCCCTTCTGCATCTATATCCTCAACCTGGCGG
CAGCCGACCTCCTCTTCCTCTTCAGCATGGCTTCCACGCTCAGCCTGGAAACCCAGCCCCTGGTCAATAC
CACTGACAAGGTCCACGAGCTGATGAAGAGACTGATGTACTTTGCCTACACAGTGGGCCTGAGCCTGCTG
ACGGCCATCAGCACCCAGCGCTGTCTCTCTGTCCTCTTCCCTATCTGGTTCAAGTGTCACCGGCCCAGGC
ACCTGTCAGCCTGGGTGTGTGGCCTGCTGTGGACGCTCTGTCTCCTGATGAACGGGTTGACCTCTTCCTT
CTGCAGCAAGTTCTTGAAATTCAATGAAGATCGGTGCTTCAGGGTGGACATGGTCCAGGCCGCCCTCATC
ATGGGGGTCTTAACCCCAGTGATGACTCTGTCCAGCCTGACCCTCTTTGTCTGGGTGCGGAGGAGCTCCC
AGCAGTGGCGGCGGCAGCCCACACGGCTGTTCGTGGTGGTCCTGGCCTCTGTCCTGGTGTTCCTCATCTG
TTCCCTGCCTCTGAGCATCTACTGGTTTGTGCTCTACTGGTTGAGCCCGCCGCCCGAGATGCAGGTCCTG
TGCTTCAGCTTGTCACGCCTCTCCTCGTCCGTAAGCAGCAGCGCCAACCCCGTCATCTACTTCCTGGTGG
GCAGCCGGAGGAGCCACAGGCTGCCCACCAGGTCCCTGGGGACTGTGCTCCAACAGGCGCTTCGCGAGGA
GCCCGAGCTGGAAGGTGGGGAGACGCCCACCGTGGGCACCAATGAGATGGGGGCTTGAGAGCC
```

The disclosed NOV7 nucleic acid sequence, localized to chromosome 11, has 413 of 676 bases (61%) identical to a gb:GENBANK-ID:HUMMAS|acc:M13150.1 mRNA from Homo sapiens (Human mas proto-oncogene mRNA, complete cds).

A disclosed NOV7 polypeptide (SEQ ID NO:24) encoded by SEQ ID NO:23 is 321 amino acid residues and is presented using the one-letter amino acid code in Table 7B. Signal P, Psort and/or Hydropathy results predict that NOV7 has a signal peptide and is likely to be localized at the plasma membrane with a certainty of 0.6000. In other embodiments, NOV7 is also likely to be localized to the golgi body with a certainty of 0.4000, to the enoplasmic reticulum (membrane) with a certainty of 0.3000, or the microbody with a certainty of 0.3000. The most likely cleavage site for a NOV7 peptide is between amino acids 44 and 45, at: MAG-NS.

Table 7B. Encoded NOV7 protein sequence (SEQ ID NO:34).

```
MNQTLNSSGTVESALNYSRGSTVHTAYLVLSSLAMFTCLCGMAGNSMVIWLLGFRMHRNPFCIYILNLAA
ADLLFLFSMASTLSLETQPLVNTTDKVHELMKRLMYFAYTVGLSLLTAISTQRCLSVLFPIWFKCHRPRH
LSAWVCGLLWTLCLLMNGLTSSFCSKFLKFNEDRCFRVDMVQAALIMGVLTPVMTLSSLTLFVWVRRSSQ
QWRRQPTRLFVVVLASVLVFLICSLPLSIYWFVLYWLSPPPEMQVLCFSLSRLSSSVSSSANPVIYFLVG
SRRSHRLPTRSLGTVLQQALREEPELEGGETPTVGTNEMGA
```

The disclosed NOV7 amino acid sequence has 114 of 318 amino acid residues (35%) identical to, and 185 of 318 amino acid residues (58%) similar to, the 324 amino acid residue ptnr:SWISSPROT-ACC:P12526 protein from Rattus norvegicus (Rat) (MAS PROTO-ONCOGENE).

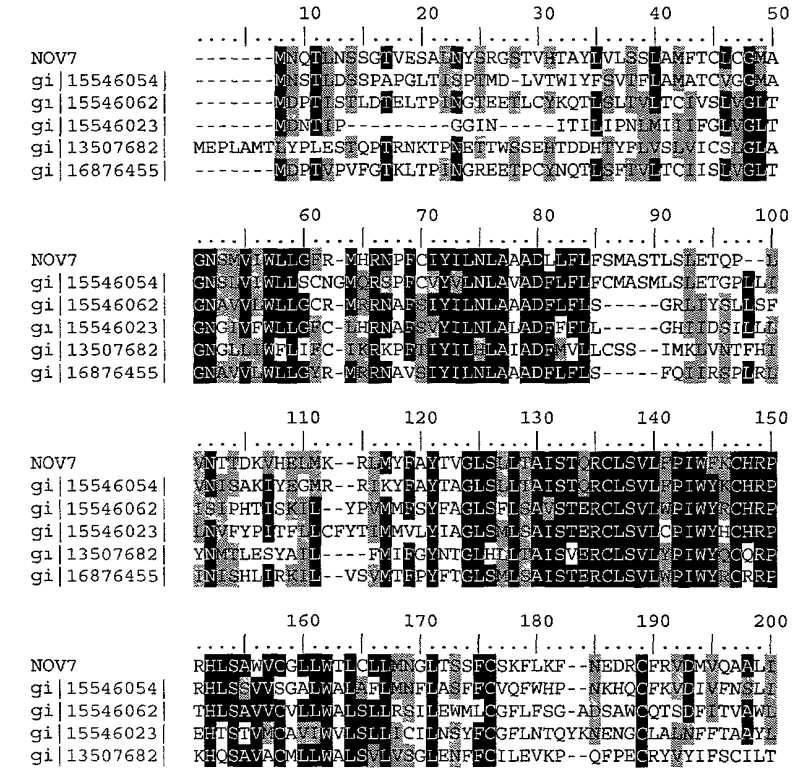
NOV7 also has homology to the amino acid sequence shown in the BLASTP data listed in Table 7C.

Table 7C. BLAST results for NOV7					
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|15546023|gb|AAK91787.1 (AY042191)	RF-amide G protein-coupled receptor [Mus musculus]	322	40	58	8e-43
gi|13507682|ref|NP_096521.1| (NM_030726)	G protein-coupled receptor 90; G-protein coupled receptor GPR90 [Mus musculus]	321	36	56	1e-40
gi|16876455|ref|NP_473373.1| (NM_054032)	G protein-coupled receptor MRGX4 [Homo sapiens]	322	41	58	2e-40
gi|15546054|gb|AAK91800.1| (AY042209)	MrgD G protein-coupled receptor [Mus musculus]	321	58	72	3e-83
gi|15546062|gb|AAK91804.1| (AY042213)	MrgX1 G protein-coupled receptor [Homo sapiens]	322	40	58	8e-43

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 7D.

Table 7D. Information for the ClustalW proteins

1) NOV7 (SEQ ID NO:34)
2) gi|15546054| (SEQ ID NO: 80)
3) gi|15546062| (SEQ ID NO: 81)
4) gi|15546023| (SEQ ID NO: 82
5) gi|13507682| (SEQ ID NO: 83)
6) gi|16876455| (SEQ ID NO: 84)



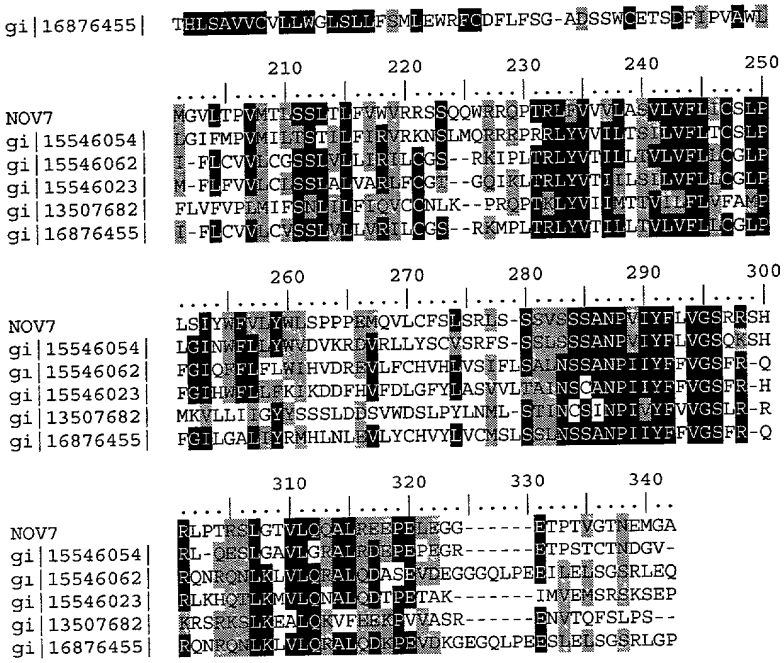


Table 7E lists the domain description from DOMAIN analysis results against NOV7. This indicates that the NOV7 sequence has properties similar to those of other proteins known to contain this domain.

Table 7E. Domain Analysis of NOV7

gnl|Pfam|pfam00001, 7tm_1, 7 transmembrane receptor (rhodopsin family).

CD-Length = 254 residues, Score = 38.9 bits (89), Expect = 5e-04

The human mas oncogene was originally detected by its ability to transform NIH 3T3 cells. We previously showed that the protein encoded by this gene is unique among cellular oncogene products in that it has seven hydrophobic potential transmembrane domains and shares strong sequence similarity with a family of hormone-receptor proteins (Young D, et.al.; Proc Natl Acad Sci U S A 1988 Jul;85(14):5339-42). We have now cloned the rat homolog of the mas oncogene, determined its DNA sequence, and examined its expression in various rat tissues. A comparison of the predicted sequences of the rat and human mas proteins shows that they are highly conserved, except in their hydrophilic amino-terminal domains. Our examination of the expression of mas, determined by RNA-protection studies, indicates that high levels of mas RNA transcripts are present in the hippocampus and cerebral cortex of the brain, but not in other neural regions or in other tissues. This pattern of expression and the

similarity of mas protein to known receptor proteins suggest that mas encodes a receptor that is involved in the normal neurophysiology and/or development of specific neural tissues.

The human mas oncogene, which renders transfected NIH/3T3 cells tumorigenic, was identified as a subtype of angiotensin receptor by transient expression in Xenopus oocytes and stable expression in the mammalian neuronal cell line, NG115-401L (Hanley MR, et.al.; Ciba Found Symp 1990;150:23-38; discussion 38-46). The mas receptor preferentially recognizes angiotensin III, and is expressed at high levels in brain. The mas/angiotensin receptor functions through the breakdown of inositol lipids and can drive DNA synthesis, unlike another inositol-linked peptide receptor, that for bradykinin. Comparative analysis of several early biochemical events elicited by either angiotensin or bradykinin stimulation of mas-transfected cells has not indicated a specific difference correlated with mitogenic activity. In particular, the inositol lipid kinase, phosphatidylinositol-3-kinase, thought to be involved in the mitogenic mechanism of platelet-derived growth factor receptors, is unaffected by activation of mas. These results have shown that a proto-oncogene encodes a neural peptide receptor, indicating that peptide receptors may be involved in differentiation and proliferation processes, as are other identified proto-oncogenes.

The class of receptors coupled to GTP-binding proteins share a conserved structural motif which is described as a 'seven-transmembrane segment' following the prediction that these hydrophobic segments form membrane-spanning alpha-helices (Jackson TR, et.al.; Nature 1988 Sep 29;335(6189):437-40). Identified examples include the mammalian opsins, alpha 1-, alpha 2-, beta 1- and beta 2-adrenergic receptors, the muscarinic receptor family, the 5-HT1C-receptor, and the substance-K receptor. In addition, two mammalian genes have been identified that code for predicted gene products with sequence similarity to these receptors, but whose ligand specificity is unknown namely, G21 and the mas oncogene. The mas oncogene shows the greatest sequence similarity to the substance-K receptor, and on this basis it was predicted that it would encode a peptide receptor with mitogenic activity which would act through the inositol lipid signalling pathways. The mas oncogene product was transiently expressed in Xenopus oocytes, and stably expressed in a transfected mammalian cell line. The results demonstrate that the mas gene product is a functional angiotensin receptor.

The disclosed NOV7 nucleic acid of the invention encoding a MAS proto-oncogene Precursor-like protein includes the nucleic acid whose sequence is provided in Table 7A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 7A while still encoding a protein that maintains its MAS proto-oncogene Precursor-like activities and physiological

functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 39 percent of the bases may be so changed.

The disclosed NOV7 protein of the invention includes the MAS proto-oncogene Precursor-like protein whose sequence is provided in Table 7B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 7B while still encoding a protein that maintains its MAS proto-oncogene Precursor-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 65 percent of the residues may be so changed.

The protein similarity information, expression pattern, and map location for the MAS proto-oncogene Precursor-like protein and nucleic acid (NOV7) disclosed herein suggest that NOV7 may have important structural and/or physiological functions characteristic of the MAS proto-oncogene Precursor-like family. Therefore, the NOV7 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications. These include serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo.

The NOV7 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below and/or other pathologies. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from hypogonadotropic hypogonadism, Kallman syndrome, bacterial/viral infection, immunological and inflammatory diseases and disorders, and/or other pathologies/disorders. The NOV7 nucleic acid, or fragments thereof, may further

be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV7 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV7 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV7 epitope is from about amino acids 20 to 80. In other embodiments, contemplated NOV7 epitopes are from amino acids 105 to 125, from amino acids 140 to 160, from amino acids 175 to 200, or from amino acids 215 to 275. This novel protein also has value in development of powerful assay system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV8

A disclosed NOV8 nucleic acid of 671 nucleotides (also referred to as AL163195_da2) encoding a novel ribonuclease pancreatic precursor-like protein is shown in Table 8A. An open reading frame was identified beginning with at nucleotides 3-5 and ending with a TAA codon at nucleotides 465-467.

Table 8A. NOV8 nucleotide sequence (SEQ ID NO:35).

```
ATGCGAAGTCACTCTTACCTCTGATGATAATAATGGTGATAATTTTCTTGGTGCTTCTGTTCTGGGAAAA
TGAGGTGAATGATGAAGCAGTGATGTCAACTTTAGAACACTTGCATGTGGACTACCCTCAGAATGACGTT
CCCGTTCCTGCAAGGTACTGCAACCACATGATCATACAAAGAGTTATCAGGGAACCTGACCACACTTGTA
AAAAGGAGCATGTCTTCATCCATGAGAGGCCTCGAAAAATCAATGGTATTTGCATTTCTCCCAAGAAGGT
TGCTTGCCAAAACCTTTCGGCCATTTTCTGCTTTCAGAGTGAGACAAAGTTCAAAATGACAGTCTGTCAG
CTCATTGAAGGCACAAGATACCCTGCCTGCAGGTACCACTATTCCCCCACAGAGGGGTTTGTTCTTGTCA
CTTGTGATGACTTGAGGCCAGATAGTTTCCTTGGCTATGTTAAATAACTCAAGATCAGCTCCCGAGTCTG
AGATCTCTTCTCTCAATGGCATTGGAGCTGGCTGTGCCTGAGGCAGACCTGGACCGTGGACATGGGGCAA
TGCCTTGAACGGAAGGGGAAGCCACTGGTAATTAATTTATCCTTCCTGTATTGCTGGGTTGGGATTGTTT
TATTCTGCTTCAATAAAATAATCTTTACTGAATTAAAAAAA
```

The NOV8 nucleic acid sequence is located on chromsome 14.

The disclosed NOV8 polypeptide (SEQ ID NO:26) encoded by SEQ ID NO:25 has 154 amino acid residues and is presented in Table 8B using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV8 has a signal peptide and is likely to be localized at the plasma membrane with a certainty of 0.6800. In other embodiments, NOV8 may also be localized to the endoplasmic reticulum (membrane) with a certainty of

0.6400, the golgi body with a certainty of 0.3700, or the endoplasmic reticulum (lumen) with a certainty of 0.1000. The most likely cleavage site for NOV8 is between positions 27 and 28, VND-EA.

Table 8B. Encoded NOV8 protein sequence (SEQ ID NO:36).

```
AKSLLPLMIIMVIIFLVLLFWENEVNDEAVMSTLEHLHVDYPQNDVPVPARYCNHMIIQRVIREPDHTCK
KEHVFIHERPRKINGICISPKKVACQNLSAIFCFQSETKFKMTVCQLIEGTRYPACRYHYSPTEGFVLVT
CDDLRPDSFLGYVK
```

A search of sequence databases reveals that the NOV8 amino acid sequence has 43 of 141 amino acid residues (30%) identical to, and 75 of 141 amino acid residues (53%) similar to, the 156 amino acid residue ptnr:SWISSPROT-ACC:P07998 protein from Homo sapiens (Human) (RIBONUCLEASE PANCREATIC PRECURSOR (EC 3.1.27.5) (RNASE 1) (RNASE A) (RNASE UPI-1) (RIB-1)).

NOV8 is found in at least lung, testis, and B-cell. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

NOV8 also has homology to the amino acid sequence shown in the BLASTP data listed in Table 8C.

Table 8C. BLAST results for NOV8

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|13399882 pdb 1DZA|A	Chain A, 3-D Structure Of A Hp-Rnase	129	30	50	5e-09
gi|12853968 dbj BAB29898.1 (AK015573)	Putative protein/mouse	208	34	54	6e-09
gi|133226|sp|P19644|RNP_PREEN	RIBONUCLEASE PANCREATIC (RNASE 1) (RNASE A)	128	34	55	6e-09
gi|464659|sp|P80287|RNP_IGUIG	RIBONUCLEASE PANCREATIC (RNASE 1) (RNASE A)	119	27	49	1e-08
gi|13124491 sp|Q9QYX3|RNP_MUSPA	RIBONUCLEASE PANCREATIC PRECURSOR (RNASE 1) (RNASE A)	149	28	50	3E-09

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 8D.

Table 8D. Information for the ClustalW proteins

1) NOV8 (SEQ ID NO:36)
2) gi|13124491| (SEQ ID NO: 85)
3) gi|13399882| (SEQ ID NO: 86)
4) gi|12853968| (SEQ ID NO: 87)
5) gi|133226| (SEQ ID NO: 88)
6) gi|464659| (SEQ ID NO: 89)

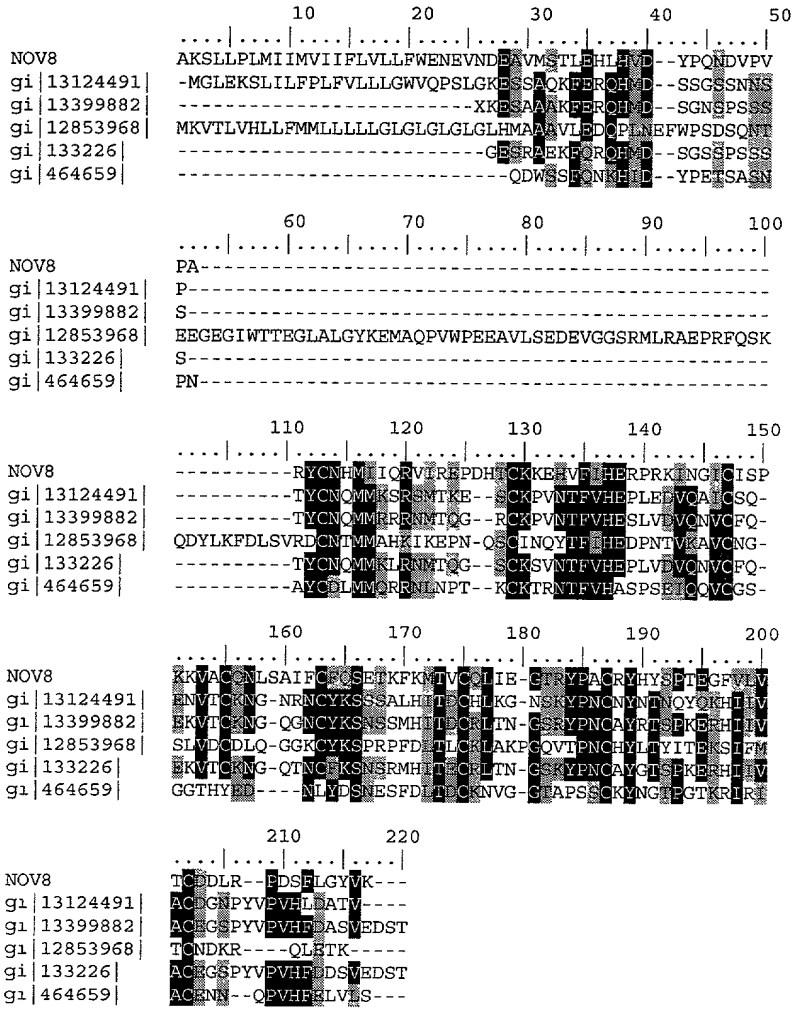


Table 8E lists the domain description from DOMAIN analysis results against NOV8. This indicates that the NOV8 sequence has properties similar to those of other proteins known to contain this domain.

Table 8E. Domain Analysis of NOV8

gnl|Smart|smart00092, RNAse_Pc, Pancreatic ribonuclease
CD-Length = 123 residues, 80.5% aligned Score = 66.6 bits (161),
Expect = 1e-12

Enzymic properties of members of the ribonuclease A superfamily, like the activity on RNA, the preference for either cytosine or racil in the primary binding site B1, the preference for the other side of the cleaved phosphodiester bond, the B2 site, and features of the two noncatalytic phosphate-binding sites P0 and P2 are discussed in several articles in this multi-author review, and are summarized in this closing article(See Beintema JJ, et.al.; Cell Mol Life Sci 1998 Aug;54(8):825-32). A special feature of members of the ribonucleases 1 family is their destabilizing action on double-stranded nucleic acid structures. A feature of the ribonuclease A superfamily is the frequent occurrence of gene duplications, both in ancestral vertebrate lineages and in recently evolved taxa. Three different bovine ribonucleases 1 have been identified in pancreas, semen and brain, respectively, which are the result of two gene duplications in an ancestral ruminant. Similar gene duplications have been identified in other ribonuclease families in several mammalian and other vertebrate taxa. The ribonuclease family, of which the human members have been assigned numbers 2, 3 and 6, underwent a still mysterious pattern of gene duplications and functional expression as proteins with ribonuclease activity and other physiological properties.

Pancreatic ribonuclease (EC 3.1.27.5) is one of the digestive enzymes secreted in abundance by the pancreas. Elliott et al. (Cytogenet. Cell Genet. 42: 110-112, 1986) mapped the mouse gene to chromosome 14 by Southern blot analysis of genomic DNA from recombinant inbred strains of mice, using a probe isolated from a pancreatic cDNA library with the rat cDNA. A polymorphic BamHI site was used to demonstrate complete concordance of the Rib-1 locus with Tcra and Np-2, encoding the alpha subunit of the T-cell receptor (186880) and nucleoside phosphorylase (164050), respectively. The assignment to mouse 14 and the close linkage to the other 2 loci was confirmed by study of one of Snell's congenic strains: the 3 loci went together. Elliott et al. (1986) predicted that the homologous human gene RIB1 is on chromosome 14.

Human pancreatic RNase is monomeric and is devoid of any biologic activity other than its RNA degrading ability. Piccoli et al. (Proc. Nat. Acad. Sci. 96: 7768-7773,1999) engineered the monomeric form into a dimeric protein with cytotoxic action on mouse and human tumor cells, but lacking any appreciable toxicity on human and mouse normal cells. The dimeric variant of human pancreatic RNase selectively sensitized cells derived from a human thyroid tumor to apoptotic death. Because of its selectivity for tumor cells, and because of its human origin, this protein was thought to represent an attractive tool for anticancer therapy.

The disclosed NOV8 nucleic acid of the invention encoding a Ribonuclease pancreatic precursor-like protein includes the nucleic acid whose sequence is provided in Table 8A, or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 8A while still encoding a protein that maintains its Ribonuclease pancreatic precursor-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 100% percent of the bases may be so changed.

The disclosed NOV8 protein of the invention includes the Ribonuclease pancreatic precursor-like protein whose sequence is provided in Table 8B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 2 while still encoding a protein that maintains its Ribonuclease pancreatic precursor-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 70% percent of the residues may be so changed.

The invention further encompasses antibodies and antibody fragments, such as F_{ab} or $(F_{ab})_2$, that bind immunospecifically to any of the proteins of the invention.

The above defined information for this invention suggests that this Ribonuclease pancreatic precursor-like protein (NOV8) may function as a member of a "Ribonuclease pancreatic precursor family". Therefore, the NOV8 nucleic acids and proteins identified here may be useful in potential therapeutic applications implicated in (but not limited to) various pathologies and disorders as indicated below. The potential therapeutic applications for this invention include, but are not limited to: protein therapeutic, small molecule drug target, antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), diagnostic and/or prognostic marker, gene therapy (gene delivery/gene ablation), research tools, tissue regeneration *in vivo* and *in vitro* of all tissues and cell types composing (but not limited to) those defined here.

The NOV8 nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in cancer including but not limited to Inflamation, Autoimmune disorders, Aging and Cancer. For example, a cDNA encoding the Ribonuclease pancreatic precursor-like protein (NOV8) may be useful in gene therapy, and the Ribonuclease pancreatic precursor-like protein (NOV8) may be useful when administered to a subject in need thereof. By way of nonlimiting example, the compositions of the present invention will have efficacy for treatment of patients suffering from Diabetes,Von Hippel-Lindau (VHL) syndrome , Pancreatitis,Obesity, Hyperthyroidism and Hypothyroidism and Cancers including, but no limited to Thyroid and Pancreas, and other such conditions. The NOV8 nucleic acid encoding Ribonuclease pancreatic precursor-like protein, and the ribonuclease pancreatic precursor-like protein of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV8 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immuno-specifically to the novel NOV8 substances for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV8 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV8 epitope is from about amino acids 5 to 25. In another embodiment, a NOV8 epitope is from about amino acids 90 to 100. These novel proteins can be used in assay systems for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV9

A disclosed NOV9 nucleic acid of 1476 nucleotides (also referred to as SC87421058_A) encoding a novel Aminotransferase-like protein is shown in Table 9A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 26-28 and ending with a TAA codon at nucleotides 1379-1381. The start and stop codons are in bold letters.

Table 9A. NOV9 nucleotide sequence (SEQ ID NO:37).

CAGGTGCAAACCAGCCCCAGGCTCC**ATG**GCTTCAAGAAGGTCGAAGTTCAAGGGAAGCACCAAGGCTCCC
TTGTGGGTCTGGAAATCTGCATTGGTAAATGCTTTAGGCTTTTTTACTTCTTCATGCAAAGTTTTCTTTG
CATCGGATCCCATCAAAATAGTGAGAGCCCAGAGGCAGTACATGTTTGATGAGAACGGTGAACAGTACTT
GGACTGCATCAACAATGTTGCCGTGGGACACTGTCACCCAGGAGTGGTCAAAGCTGCCCTGAAACAGATG

GAACTGCTAAATACAAATTCTCGATTCCTCCACGACAACATTGTTGAGTATGCCAAACGCCTTTCAGCAA
CTCTGCCGGAGAAACTCTCTGTTTGTTATTTTACAAATTCAGGGTCCGAAGCCAACGACTTAGCCTTACG
CCTGGCTCGGCAGTTCAGAGGCCACCAGGATGTGATCACTCTTGACGCTTACCATGGTCACCTATCATCC
TTAATTGAGATTAGCCCATATAAGTTTCAGAAAGGAAAAGATGTCAAAAAAGAATTTGTACATGTGGCAC
CAACTCCAGATACTTACAGAGGAAAATATAGAGAAGACCATGCAGACTCAGCCAGTGCTTATGCAGATGA
AGTGAAGAAAATCATTGAAGATGCTCATAACAGTGGAAGGAAGGTTGCTGCCTTTATTGCTGAATCCATG
CAGAGTTGTGGCGGACAAATAATTCCTCCAGCAGGCTACTTCCAGAAAGTGGCAGAGTATGTACACGGTG
CAGGGGGTGTGTTTATAGCTGATGAAGTTCAAGTGGGCTTTGGCAGAGTTGGGAAACATTTCTGGAGCTT
CCAGATGTATGGTGAAGACTTTGTTCCAGACATCGTCACAATGGGAAAACCGATGGGCAACGGCCACCCG
GTGGCATGTGTGGTAACAACCAAAGAAATTGCAGAAGCCTTCAGCAGCTCTGGGATGGAATATTTTAATA
CGTATGGAGGAAATCCAGTATCTTGTGCTGTTGGTTTGGCTGTCCTGGATATAATTGAAAATGAAGACCT
TCAAGGAAATGCCAAGAGAGTAGGGAATTATCTCACTGAGTTACTGAAAAAACAGAAGGCTAAACACACT
TTGATAGGAGATATTAGGGGCATTGGCCTTTTTATTGGAATTGATTTAGTGAAGGACCATCTGAAAAGGA
CCCCTGATATGTATTTAGCTTTGGGGACAATTTTGGTTCTGGAGAAAGAAAAACGAGTGCTTCTCAGTGC
CGATGGACCTCATAGAAATGTACTTAAAATAAAACCACCTATGTGCTTCACTGAAGAAGATGCAAAGTTC
ATGGTGGACCAACTTGATAGGATTCTAACAGGTGGGTCCATGGATCTT**TAA**GATGTCTTCTTGTTCCCTC
TCCCAAACCCACCCCTCAAACCCTGGTCTAGTCATAATGAGCATATGCATCTTGTTATTCATGATGGAAG
TGAGGC

The disclosed NOV9 nucleic acid sequence, localized to chromosome 4, has 342 of 540 bases (63%) identical to a gb:GENBANK-ID:AK023470|acc:AK023470.1 mRNA from Homo sapiens (Homo sapiens cDNA FLJ13408 fis, clone PLACE1001672, weakly similar to PROBABLE AMINOTRANSFERASE T01B11.2 (EC 2.6.1.-).

The disclosed NOV9 polypeptide (SEQ ID NO:28) encoded by SEQ ID NO:27 has 451 amino acid residues and is presented in Table 9B using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV9 has a signal peptide and is likely to be localized in the mitochondrial matrix space with a certainty of 0.5365. In other embodiments, NOV9 may also be localized to the nucleus with a certainty of 0.3600, the microbody with a certainty of 0.2667, or the mitochondrial inner membrane with a certainty of 0.2612. The most likely cleavage site for NOV9 is between positions 34 and 35, SSC-KV.

Table 9B. Encoded NOV9 protein sequence (SEQ ID NO:38).

MASRRSKFKGSTKAPLWVWKSALVNALGFFTSSCKVFFASDPIKIVRAQRQYMFDENGEQYLDCINNVAV
GHCHPGVVKAALKQMELLNTNSRFLHDNIVEYAKRLSATLPEKLSVCYFTNSGSEANDLALRLARQFRGH
QDVITLDAYHGHLSSLIEISPYKFQKGKDVKKEFVHVAPTPDTYRGKYREDHADSASAYADEVKKIIEDA
HNSGRKVAAFIAESMQSCGGQIIPPAGYFQKVAEYVHGAGGVFIADEVQVGFGRVGKHFWSFQMYGEDFV
PDIVTMGKPMGNGHPVACVVTTKEIAEAFSSSGMEYFNTYGGNPVSCAVGLAVLDIIENEDLQGNAKRVG
NYLTELLKKQKAKHTLIGDIRGIGLFIGIDLVKDHLKRTPDMYLALGTILVLEKEKRVLLSADGPHRNVL
KIKPPMCFTEEDAKFMVDQLDRILTGGSMDL

A search of sequence databases reveals that the NOV9 amino acid sequence has 197 of 340 amino acid residues (57%) identical to, and 256 of 340 amino acid residues (75%) similar to, the 474 amino acid residue ptnr:SPTREMBL-ACC:Q9VU95 protein from Drosophila melanogaster (Fruit fly) (CG8745 PROTEIN).

NOV9 is expressed in the brain and the hypothalamus.

The disclosed NOV9 polypeptide has homology to the amino acid sequences shown in the BLASTP data listed in Table 9C.

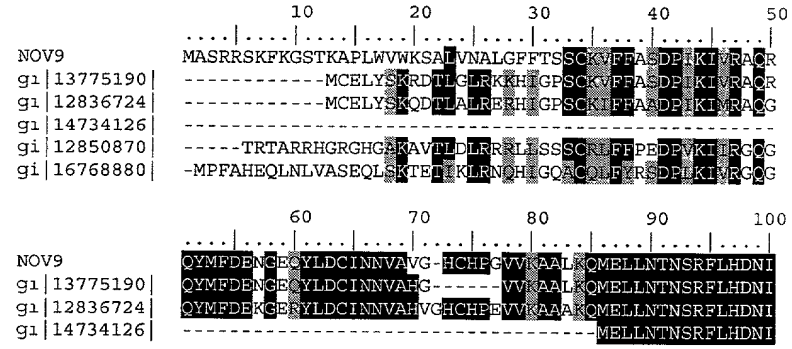
Table 9C. BLAST results for NOV9

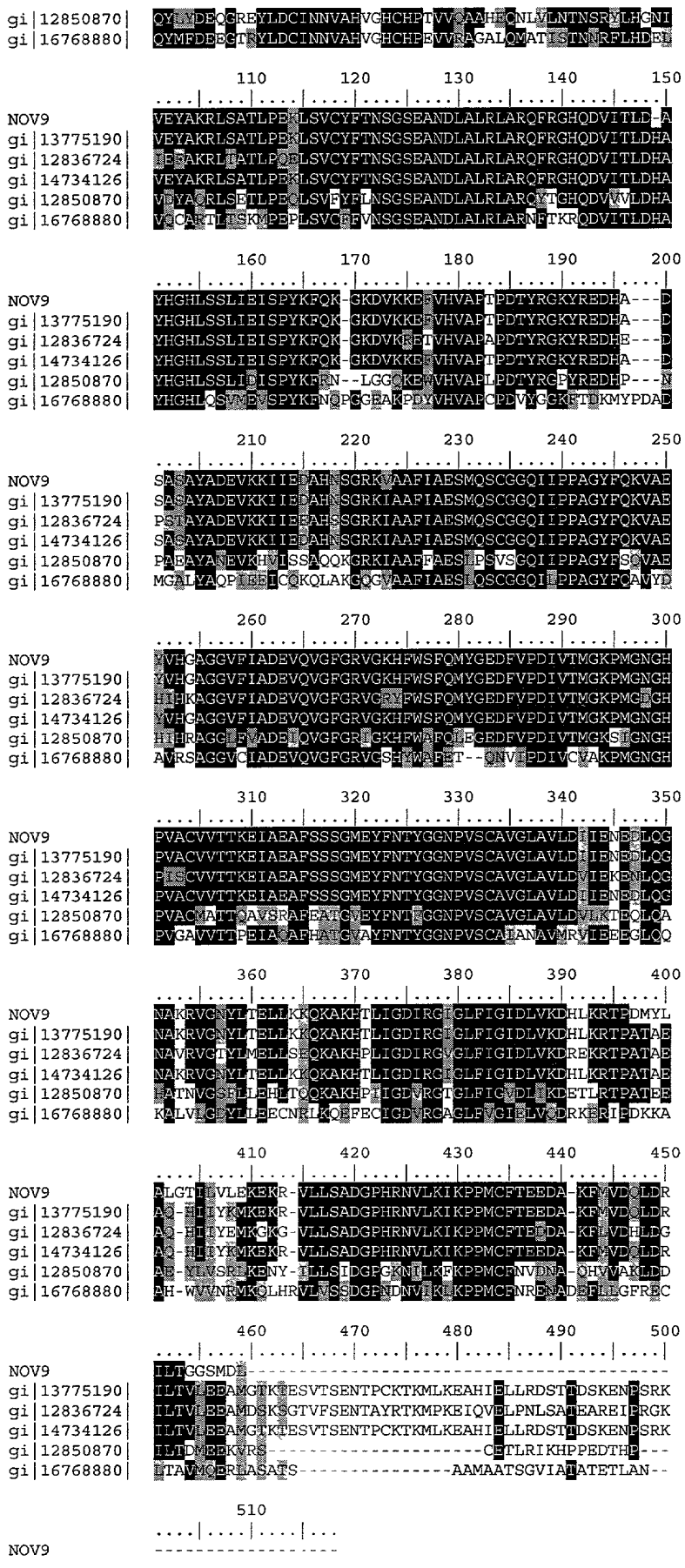
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|13775190 ref NP 112569.1 (NM_031279)	alanine-glyoxylate aminotransferase 2-like 1 [Homosapiens]	493	95	95	0.0
gi|12836724 db BAB 23784.1 (AK005060)	Putative protein/mouse	499	85	91	0.0
gi|14734126 ref XP 034659.1 (XM_034659)	alanine-glyoxylate aminotransferase 2-like 1 [Homo sapiens]	426	96	96	0.0
gi|12850870 db BAB 28878.1 (AK013489)	Putative protein/mouse	473	65	80	e-164
gi|16768880 gb|AAL2 8659.1 (AY061111)	LD09584p [Drosophila melanogaster]	494	58	74	e-138

The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 9D. In the ClustalW alignment of the NOV9 protein, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties), whereas non-highlighted amino acid residues are less conserved and can potentially be altered to a much broader extent without altering protein structure or function.

Table 9D. ClustalW Analysis of NOV9

1) Novel NOV9 (SEQ ID NO:38)
2) gi|13775190| (SEQ ID NO: 90)
3) gi|12836724| (SEQ ID NO: 91)
4) gi|14734126| (SEQ ID NO: 92)
5) gi|12850870| (SEQ ID NO: 93)
6) gi|16768880| (SEQ ID NO: 94)




gi|12850870|
gi|16768880|
NOV9
gi|13775190|
gi|12836724|
gi|14734126|
gi|12850870|
gi|16768880|

```
gi|13775190|   RNGMCTDTHSLLSKRLKT
gi|12836724|   RNGVCSDQQALLSKRLKT
gi|14734126|   RNGMCTDTHSLLSKRLKT
gi|12850870|   -------TQILLTRQQD-
gi|16768880|   -KTKLFERQDRLIKSV--
```

Table 9E lists the domain description from DOMAIN analysis results against NOV9. This indicates that the NOV9 sequence has properties similar to those of other proteins known to contain this domain.

Table 9E. Domain Analysis of NOV9

gnl|Pfam|pfam00202, aminotran_3, Aminotransferase class-III

CD-Length = 406 residues, 96.6% aligned

Score = 266 bits (681), Expect = 1e-72

A disclosed NOV9 nucleic acid encodes for a novel member of the Transferase superfamily of enzymes. Specifically, the sequence encodes a amino-transferase-like protein. Amino-transferase enzymes play crucial roles in liver metabolism. Serum amino-transferase concentrations have been used as an accurate diagnostic measure in cases of liver toxicity and damage such as in liver cancer, cirrhosis due to alcohol abuse, or troglitazone treatment for diabetes. For this reason the enzymes of the amino-transferase superfamily are potentially useful as diagnostic indicators. The protein described here is known to be expressed in brain tissue, which may indicate a role in brain and CNS disorders. The amino-transferase-like protein (NOV9; SC87421058_A) described here could be used in diagnostic tools to detect liver damage due to cirrhosis, cancer, or chemical toxicity; or to detect or treat certain brain and CNS pathologies.

Acute hormonal regulation of liver carbohydrate metabolism mainly involves changes in the cytosolic levels of cAMP and Ca2+. Epinephrine, acting through beta 2-adrenergic receptors, and glucagon activate adenylate cyclase in the liver plasma membrane through a mechanism involving a guanine nucleotide-binding protein that is stimulatory to the enzyme. The resulting accumulation of cAMP leads to activation of cAMP-dependent protein kinase, which, in turn, phosphorylates many intracellular enzymes involved in the regulation of glycogen metabolism, gluconeogenesis, and glycolysis. These are (1) phosphorylase b kinase, which is activated and, in turn, phosphorylates and activates phosphorylase, the rate-limiting enzyme for glycogen breakdown; (2) glycogen synthase, which is inactivated and is rate-controlling for glycogen synthesis; (3) pyruvate kinase, which is inactivated and is an important regulatory enzyme for glycolysis; and (4) the 6-phosphofructo-2-kinase/fructose

2,6-bisphosphatase bifunctional enzyme, phosphorylation of which leads to decreased formation of fructose 2,6-P2, which is an activator of 6-phosphofructo-1-kinase and an inhibitor of fructose 1,6-bisphosphatase, both of which are important regulatory enzymes for glycolysis and gluconeogenesis. In addition to rapid effects of glucagon and beta-adrenergic agonists to increase hepatic glucose output by stimulating glycogenolysis and gluconeogenesis and inhibiting glycogen synthesis and glycolysis, these agents produce longer-term stimulatory effects on gluconeogenesis through altered synthesis of certain enzymes of gluconeogenesis/glycolysis and amino acid metabolism. For example, P-enolpyruvate carboxykinase is induced through an effect at the level of transcription mediated by cAMP-dependent protein kinase. Tyrosine amino-transferase, serine dehydratase, tryptophan oxygenase, and glucokinase are also regulated by cAMP, in part at the level of specific messenger RNA synthesis. The sympathetic nervous system and its neurohumoral agonists epinephrine and norepinephrine also rapidly alter hepatic glycogen metabolism and gluconeogenesis acting through alpha 1-adrenergic receptors. The primary response to these agonists is the phosphodiesterase-mediated breakdown of the plasma membrane polyphosphoinositide phosphatidylinositol 4,5-P2 to inositol 1,4,5-P3 and 1,2-diacylglycerol. This involves a guanine nucleotide-binding protein that is different from those involved in the regulation of adenylate cyclase. Inositol 1,4,5-P3 acts as an intracellular messenger for Ca2+ mobilization by releasing Ca2+ from the endoplasmic reticulum.

The disclosed NOV9 nucleic acid of the invention encoding a Aminotransferase-like protein includes the nucleic acid whose sequence is provided in Table 9A, or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 9A while still encoding a protein that maintains its Aminotransferase-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 37 percent of the bases may be so changed.

The disclosed NOV9 protein of the invention includes the Aminotransferase-like protein whose sequence is provided in Table 9B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 2 while still encoding a protein that maintains its Aminotransferase-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 43 percent of the residues may be so changed.

The invention further encompasses antibodies and antibody fragments, such as F_{ab} or $(F_{ab})_2$, that bind immunospecifically to any of the proteins of the invention.

The above defined information for this invention suggests that this Aminotransferase-like protein (NOV9) may function as a member of a "Aminotransferase family". Therefore, the NOV9 nucleic acids and proteins identified here may be useful in potential therapeutic applications implicated in (but not limited to) various pathologies and disorders as indicated below. The potential therapeutic applications for this invention include, but are not limited to: protein therapeutic, small molecule drug target, antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), diagnostic and/or prognostic marker, gene therapy (gene delivery/gene ablation), research tools, tissue regeneration *in vivo* and *in vitro* of all tissues and cell types composing (but not limited to) those defined here.

The NOV9 nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in liver toxicity and damage such as in cancer, cirrhosis, or troglitazone treatment for diabetes; brain and CNS disorders including cancer, Parkinson's, Alzheimer's, epilepsy, schizophrenia and other diseases, disorders and conditions of the like. For example, a cDNA encoding the Aminotransferase-like protein (NOV9) may be useful in gene therapy, and the Aminotransferase-like protein (NOV9) may be useful when administered to a subject in need thereof. By way of nonlimiting example, the compositions of the present invention will have efficacy for treatment of patients suffering from bacterial, fungal, protozoal and viral infections (particularly infections caused by HIV-1 or HIV-2), pain, cancer (including but not limited to Neoplasm; adenocarcinoma; lymphoma; prostate cancer; uterus cancer), anorexia, bulimia, asthma, Parkinson's disease, acute heart failure, hypotension, hypertension, urinary retention, osteoporosis, Crohn's disease; multiple sclerosis; and Treatment of Albright Hereditary Ostoeodystrophy, angina pectoris, myocardial infarction, ulcers, asthma, allergies, benign prostatic hypertrophy, and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation. Dentatorubro-pallidoluysian atrophy(DRPLA) Hypophosphatemic rickets, autosomal dominant (2) Acrocallosal syndrome and dyskinesias, such as Huntington's disease

or Gilles de la Tourette syndrome, and/or other pathologies or conditions. The NOV9 nucleic acid encoding Aminotransferase-like protein, and the Aminotransferase-like protein of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV9 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immuno-specifically to the novel NOV9 substances for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV9 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV9 epitope is from about amino acids 10 to 40. In another embodiment, a NOV9 epitope is from about amino acids 60 to 75. In alterative embosiments, a NOV9 epitope is from about amino acids 210 to 250, from about amino acids 310 to 340, and from about amino acids 360 to 390. These novel proteins can be used in assay systems for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV10

NOV10 includes two tolloid-like 2-like proteins disclosed below. The disclosed sequences have been named NOV10a and NOV10b.

NOV10a

A disclosed NOV10A nucleic acid of 3350 nucleotides (also referred to as CG50235-01) encoding a novel Tolloid-like 2-like protein is shown in Table 10A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 365-367 and ending with a TAG codon at nucleotides 3341-3343. The start and stop codons are in bold letters.

Table 10A. NOV10A nucleotide sequence (SEQ ID NO:39).

CGCCCATTGGCTCCTCAGCCAAGCACGTACACCAAATGTCTGAACCTGCGGTTCCTCTCGTACTGAGCAGGATTACCATG
GCAACAACACATCATCAGTAGGGTAAAACTAACCTGTCTCACGACGGTCTAAACCCAGGCAGCCTCGGCCGCCGGGCAAG
TAGCTCCGAGCGGCTGCTTCCCGGTTGCCTCGAAGAAGACAGGGGGCGCCGCGCTCCGCTTGCTCCGCGCCTGAGCCATG
CCCAGCAGCCCTGTGTAACCACCGAGTCCCGGCCGGAGCCGACCGACCCAGTGTGCGCCGTCTTTCGGCCGAGCTGAGCT
TTCGTGCACGCAACTCCCTCTGCCCCAGCCGGCCCCGCGCCACC**ATG**CCCCGGGCGACTGCACTTGGGGCCCTGGTGTCA
CTGCTGCTGCTGCTGCCGCTGCCTCGCGGCGCCGGGGGACTCGGGGAGCGCCCGGACGCCACCGCAGACTACTCAGAGCT
GGACGGCGAGGAGGGCACGGAGCAGCAGCTGGAGCATTACCACGACCCTTGCAAAGCCGCTGTCTTTTGGGGAGACATTG
CCTTAGATGAAGATGACTTGAAGCTGTTTCACATTGACAAAGCCAGAGACTGGACCAAGCAGACAGTGGGGGCAACAGGA
CACAGCACAGGTGGGCTTGAAGAGCAGGCATCTGAGAGCAGCCCAGACACCACAGCCATGGACACTGGCACCAAGGAAGC
TGGAAAGGATGGCCGGGAGAATACCACACTCCTGCACAGCCCTGGGACCTTGCATGCCGCAGCCAAGACCTTCTCTCCCC
GGGTCCGAAGAGCCACAACCTCAAGGACAGAGAGGATATGGCCTGGAGGAGTCATCCCCTACGTCATTGGAGGGAACTTC
ACTGGGAGCCAGAGGGCCATTTTTAAGCAGGCCATGAGACACTGGGAGAAGCACACCTGTGTGACCTTCATAGAAAGGAC

GGATGAGGAAAGCTTTATTGTATTCAGTTACAGAACCTGTGGCTGTTGCTCCTATGTTGGGCGCCGAGGAGGAGGCCCAC
AGGCCATATCCATTGGGAAGAACTGTGACAAGTTTGGCATTGTGGCTCACGAGCTGGGCCATGTGGTTGGGTTTTGGCAT
GAACACACCCGGCCAGACAGAGACCAACATGTCACCATCATCAGGGAAAACATCCAGCCAGGTCAGGAGTATAATTTCTT
AAAAATGGAAGCTGGGGAAGTGAGCTCTCTGGGAGAGACATACGACTTTGACAGCATCATGCACTACGCCCGGAACACCT
TCTCAAGAGGAGTTTTCTTAGACACCATCCTTCCCCGTCAAGATGACAATGGCGTCAGGCCAACCATTGGCCAGCGCGTG
CGGCTCAGTCAGGGAGACATAGCTCAAGCCCGGAAGCTGTACAAATGCCCAGCGTGTGGGGAGACCCTGCAGGACACAAC
GGGAAACTTTTCTGCACCTGGTTTCCCAAATGGGTACCCATCTTACTCCCACTGCGTCTGGAGGATCTCGGTCACCCCAG
GGGAAAAGATCGTATTAAACTTCACATCCATGGATTTGTTTAAAAGCCGACTGTGCTGGTATGATTACGTGGAGGTCCGG
GATGGTTACTGGAGAAAAGCCCCCCTTTTGGGCAGGTTTTGTGGCGATAAGATCCCGGAGCCCCTCGTCTCCACGGACAG
CCGGCTCTGGGTGGAGTTCCGCAGCAGCAGCAACATCTTGGGCAAGGGCTTCTTTGCAGCGTACGAAGCTACCTGCGGGG
GAGACATGAACAAAGATGCCGGTCAGATTCAATCTCCCAACTATCCGGATGACTACAGACCTTCCAAGGAATGTGTCTGG
AGGATTACGGTTTCAGAGGGGTTTCACGTGGGACTTACCTTCCAAGCTTTTGAGATTGAAAGGCACGACAGCTGTGCATA
TGACTACCTGGAAGTCCGGGATGGCCCCACGGAAGAGAGTGCCCTGATCGGCCACTTTTGTGGCTATGAGAAGCCGGAGG
ATGTGAAATCGAGCTCCAACAGACTGTGGATGAAGTTTGTGTCCGATGGCTCTATCAATAAAGCGGGCTTTGCAGCCAAT
TTTTTCAAGGAGGTGGATGAGTGTTCCTGGCCAGATCACGGCGGGTGCGAACATCGCTGTGTGAACACGCTGGGCAGCTA
CAAGTGTGCCTGTGACCCTGGCTACGAGCTGGCCGCCGATAAGAAGATGTGTGAAGTGGCCTGTGGCGGTTTCATTACCA
AGCTGAATGGAACCATCACCAGCCCTGGGTGGCCGAAGGAGTATCCCACAAACAAAAACTGTGTCTGGCAGGTGGTGGCC
CCCACTCAGTACCGGATCTCCCTTCAGTTTGAAGTGTTTGAACTGGAAGGCAATGACGTCTGTAAGTACGACTTTGTAGA
GGTGCGCAGCGGCCTGTCCCCCGACGCCAAGCTGCACGGCAGGTTCTGCGGCTCTGAGACGCCGGAAGTCATCACCTCGC
AGAGCAACAACATGCGCGTGGAGTTCAAGTCCGACAACACCGTCTCCAAGCGCGGCTTCAGGGCCCACTTCTTCTCAGAT
AAGGACGAGTGTGCCAAGGACAACGGCGGGTGTCAGCATGAGTGCGTCAACACCTTCGGGAGCTACCTGTGCAGGTGCAG
AAACGGCTACTGGCTCCACGAGAATGGGCATGACTGCAAAGAGGCTGGCTGTGCACACAAGATCAGCAGTGTGGAGGGGA
CCCTGGCGAGCCCCAACTGGCCTGACAAATACCCCAGCCGGAGGGAGTGTACCTGGAACATCTCTTCGACTGCAGGCCAC
AGAGTGAAACTCACCTTTAATGAGTTTGAGATCGAGCAGCACCAGGAATGTGCCTATGACCACCTGGAAATGTATGACGG
GCCGGACAGCCTGGCCCCCATTCTGGGCCGTTTCTGCGGCAGCAAGAAACCAGACCCCACGGTGGCTTCCGGCAGCAAGT
GCGGGGGCAGGCTGAAGGCTGAAGTGCAGACCAAAGAGCTCTATTCCCACGCCCAGTTTGGGGACAACAACTACCCGAGC
GAGGCCCGCTGTGACTGGGTGATCGTGGCAGAGGACGGCTACGGCGTGGAGCTGACATTCCGGACCTTTGAGGTTGAGGA
GGAGGCCGACTGCGGCTACGACTACATGGAAGCCTACGACGGCTACGACAGCTCAGCGCCCAGGCTCGGCCGCTTCTGTG
GCTCTGGGCCATTAGAAGAAATCTACTCTGCAGGTGATTCCCTGATGATTCGATTCCGCACAGATGACACCATCAACAAG
AAAGGCTTTCATGCCCGATACACCAGCACCAAGTTCCAGGATGGCCTGCACATGAAGAAA**TAG**TGCTGAT

In a search of public sequence databases, the NOV10A nucleic acid sequence, which maps to chromosome 10, has 2955 of 2957 bases (99%) identical to a gb:GENBANK-ID:AF059516|acc:AF059516.1 mRNA from Homo sapiens (Homo sapiens tolloid-like 2 protein (TLL2) mRNA, complete cds).

The disclosed NOV10A polypeptide (SEQ ID NO:30) encoded by SEQ ID NO:29 has 992 amino acid residues and is presented in Table 10B using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV10A has a signal peptide and is likely to be localized extracellularly with a certainty of 0.7523. In other embodiments, NOV10A may also be localized to the microbody (peroxisome) with acertainty of 0.2280, the lysosome (lumen) with a certainty of 0.1900, or in the endoplasmic reticulum (membrane) with a certainty of 0.1000.

Table 10B. Encoded NOV10A protein sequence (SEQ ID NO:40).

MPRATALGALVSLLLLLPLPRGAGGLGERPDATADYSELDGEEGTEQQLEHYHDPCKAAVFWGDIALDED
DLKLFHIDKARDWTKQTVGATGHSTGGLEEQASESSPDTTAMDTGTKEAGKDGRENTTLLHSPGTLHAAA
KTFSPRVRRATTSRTERIWPGGVIPYVIGGNFTGSQRAIFKQAMRHWEKHTCVTFIERTDEESFIVFSYR
TCGCCSYVGRRGGGPQAISIGKNCDKFGIVAHELGHVVGFWHEHTRPDRDQHVTIIRENIQPGQEYNFLK
MEAGEVSSLGETYDFDSIMHYARNTFSRGVFLDTILPRQDDNGVRPTIGQRVRLSQGDIAQARKLYKCPA
CGETLQDTTGNFSAPGFPNGYPSYSHCVWRISVTPGEKIVLNFTSMDLFKSRLCWYDYVEVRDGYWRKAP
LLGRFCGDKIPEPLVSTDSRLWVEFRSSSNILGKGFFAAYEATCGGDMNKDAGQIQSPNYPDDYRPSKEC
VWRITVSEGFHVGLTFQAFEIERHDSCAYDYLEVRDGPTEESALIGHFCGYEKPEDVKSSSNRLWMKFVS
DGSINKAGFAANFFKEVDECSWPDHGGCEHRCVNTLGSYKCACDPGYELAADKKMCEVACGGFITKLNGT

ITSPGWPKEYPTNKNCVWQVVAPTQYRISLQFEVFELEGNDVCKYDFVEVRSGLSPDAKLHGRFCGSETP
EVITSQSNNMRVEFKSDNTVSKRGFRAHFFSDKDECAKDNGGCQHECVNTFGSYLCRCRNGYWLHENGHD
CKEAGCAHKISSVEGTLASPNWPDKYPSRRECTWNISSTAGHRVKLTFNEFEIEQHQECAYDHLEMYDGP
DSLAPILGRFCGSKKPDPTVASGSKCGGRLKAEVQTKELYSHAQFGDNNYPSEARCDWVIVAEDGYGVEL
TFRTFEVEEEADCGYDYMEAYDGYDSSAPRLGRFCGSGPLEEIYSAGDSLMIRFRTDDTINKKGFHARYT
STKFQDGLHMKK

A search of sequence databases reveals that the NOV10A amino acid sequence has 868 of 879 amino acid residues (98%) identical to, and 868 of 879 amino acid residues (98%) similar to, the 1015 amino acid residue ptnr:SPTREMBL-ACC:Q9Y6L7 protein from Homo sapiens (Human) (TOLLOID-LIKE 2 PROTEIN).

NOV10A is expressed in at least the colon, lung, parotid salivary glands and whole organism.

NOV10b

A disclosed NOV10B nucleic acid of 3146 nucleotides (also referred to as CG50235-03) encoding a novel Tolloid-like 2-like protein is shown in Table 10A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 227-229 and ending with a TAG codon at nucleotides 3137-3139. The start and stop codons are in bold letters.

Table 10C. NOV10B nucleotide sequence (SEQ ID NO:41).

GCAGCCTCGGCCGCCGGGCAAGTAGCTCCGAGCGGCTGCTTCCCGGTTGCCTCGACGAAG
ACAGGGGGCGCCGCGCTCCGCTTGCTCCGCGCCTGAGCCATGCCCAGCAGCCCTGTGTAA
CCACCGAGTCCCGGCCGGAGCCGACCGACCCAGTGTGCGCCGTCTTTCGGCCGAGCTGAG
CTTTCGTGCACGCAACTCCCTCTGCCCCAGCCGGCCCCGCGCCACC**ATG**CCCCGGGCGAC
TGCACTTGGGGCCCTGGTGTCACTGCTGCTGCTGCTGCCGCTGCCTCGCGGCGCCGGGGG
ACTCGGGGAGCGCCCGGACGCCACCGCAGACTACTCAGAGCTGGACGGCGAGGAGGGCAC
GGAGCAGCAGCTGGAGCATTACCACGACCCTTGCAAAGCCGCTGTCTTTTGGGGAGACAT
TGCCTTAGATGAAGATGACTTGAAGCTGTTTCACATTGACAAAGCCAGAGACTGGACCAA
GCAGACAGTGGGGGCAACAGGACACAGCACAGGTGGGCTTGAAGAGCAGGCATCTGAGAG
CAGCCCAGACACCACAGCCATGGACACTGGCACCAAGGAAGCTGGAAAGGGGAGCCAGAG
GGCCATTTTTAAGCAGGCCATGAGACACTGGGAGAAGCACACCTGTGTGACCTTCATAGA
AAGGACGGATGAGGAAAGCTTTATTGTATTCAGTTACAGAACCTGTGGCTGTTGCTCCTA
TGTTGGGCGCCGAGGAGGAGGCCCACAGGCCATATCCATTGGGAAGAACTGTGACAAGTT
TGGCATTGTGGCTCACGAGCTGGGCCATGTGGTTGGGTTTTGGCATGAACACACCCGGCC
AGACAGAGACCAACATGTCACCATCATCAGGGAAAACATCCAGCCAGGTCAGGAGTATAA
TTTCTTAAAAATGGAAGCTGGGGAAGTGAGCTCTCTGGGAGAGACATACGACTTTGACAG
CATCATGCACTACGCCCGGAACACCTTCTCAAGAGGAGTTTTTTTAGACACCATCCTTCC
CCGTCAAGATGACAATGGCGTCAGGCCAACCATTGGCCAGCGCGTGCGGCTCAGTCAGGG
AGACATAGCTCAAGCCCGGAAGCTGTACAAATGCCCAGGTCCTACTTGTGCTTTTGTTAG
CCAGAAAACATCAATCTGCTTGCTACACTTCTCACCAACCTGTTCCGAGGGCTTTGGCTG
GCAAAGGGCGTGTGGGGAGACCCTGCAGGACACAACGGGAAACTTTTCTGCACCTGGTTT
CCCAAATGGGTACCCATCTTACTCCCACTGCGTCTGGAGGATCTCGGTCACCCCAGGGGA
AAAGATCGTATTAAACTTCACATCCATGGATTTGTTTAAAAGCCGACTGTGCTGGTATGA
TTACGTGGAGGTCCGGGATGGTTACTGGAGAAAAGCCCCCCTTTTGGGCAGGTTTTGTGG
CGATAAGATCCCGGAGCCCCTCGTCTCCACGGACAGCCGGCTCTGGGTGGAGTTCCGCAG
CAGCAGCAACATCTTGGGCAAGGGCTTCTTTGCAGCGTACGAAGCTACCTGCGGGGGAGA
CATGAACAAAGATGCCGGTCAGATTCAATCTCCCAACTATCCGGATGACTACAGACCTTC
CAAGGAATGTGTCTGGAGGATTACGGTTTCAGAGGGGTTTCACGTGGGACTTACCTTCCA
AGCTTTTGAGATTGAAAGGCACGACAGCTGTGCATATGACTACCTGGAAGTCCGGGATGG
CCCCACGGAAGAGAGTGCCCTGATCGGCCACTTTTGTGGCTATGAGAAGCCGGAGGATGT
GAAATCGAGCTCCAACAGACTGTGGATGAAGTTTGTGTCCGATGGCTCTATCAATAAAGC
GGGCTTTGCAGCCAATTTTTTCAAGGAGGTGGATGAGTGTTCCTGGCCAGATCACGGCGG

GTGCGAGCATCGCTGTGTGAACACGCTGGGCAGCTACAAGTGTGCCTGTGACCCTGGCTA
CGAGCTGGCCGCCGATAAGAAGATGTGTGAAGTGGCCTGTGGCGGTTTCATTACCAAGCT
GAATGGAACCATCACCAGCCCTGGGTGGCCGAAGGAGTATCCCACAAACAAAAACTGTGT
CTGGCAGGTGGTGGCCCCCACTCAGTACCGGATCTCCCTTCAGTTTGAAGTGTTTGAACT
GGAAGGCAATGACGTCTGTAAGTACGACTTTGTAGAGGTGCGCAGCGGCCTGTCCCCCGA
CGCCAAGCTGCACGGCAGGTTCTGCGGCTCTGAGACGCCGGAGGTCATCACCTCGCAGAG
CAACAACATGCGCGTGGAGTTCAAGTCCGACAACACCGTCTCCAAGCGCGGCTTCAGGGC
CCACTTCTTCTCAGATAAGGACGAGTGTGCCAAGGACAACGGCGGGTGTCAGCATGAGTG
CGTCAACACCTTCGGGAGCTACCTGTGCAGGTGCAGAAACGGCTACTGGCTCCACGAGAA
TGGGCATGACTGCAAAGAGGCTGGCTGTGCACACAAGATCAGCAGTGTGGAGGGGACCCT
GGCGAGCCCCAACTGGCCTGACAAATACCCCAGCCGGAGGGAGTGTACCTGGAACATCTC
TTCGACTGCAGGCCACAGAGTGAAACTCACCTTTAATGAGTTTGAGATCGAGCAGCACCA
GGAATGTGCCTATGACCACCTGGAAATGTATGACGGGCCGGACAGCCTGGCCCCCATTCT
GGGCCGTTTCTGCGGTAGCAAGAAACCAGACCCCACGGTGGCTTCCGGCAGCAAGTGCGG
GGGCAGGCTGAAGGCTGAAGTGCAGACCAAAGAGCTCTATTCCCACGCCCAGTTTGGGGA
CAACAACTACCCGAGCGAGGCCCGCTGTGACTGGGTGATCGTGGCAGAGGACGGCTACGG
CGTGGAGCTGACATTCCGGACCTTTGAGGTTGAGGAGGAGGCCGACTGCGGCTACGACTA
CATGGAAGCCTACGACGGCTACGACAGCTCAGCGCCCAGGCTCGGCCGCTTCTGTGGCTC
TGGGCCATTAGAAGAAATCTACTCTGCAGGTGATTCCCTGATGATTCGATTCCGCACAGA
TGACACCATCAACAAGAAAGGCTTTCATGCCCGATACACCAGCACCAAGTTCCAGGATGC
CCTGCACATGAAGAAA**TAG**TGCTGAT

In a search of public sequence databases, the NOV10B nucleic acid sequence, which maps to chromosome 10, has 1882 of 1884 bases (99%) identical to a gb:GENBANK-ID:AK026106|acc:AK026106.1 mRNA from Homo sapiens (Homo sapiens cDNA: FLJ22453 fis, clone HRC09679, highly similar to AF059516 Homo sapiens tolloid-like 2 protein (TLL2) mRNA).

The disclosed NOV10B polypeptide (SEQ ID NO:30) encoded by SEQ ID NO:29 has 970 amino acid residues and is presented in Table 10B using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV10B has a signal peptide and is likely to be localized extracellularly with a certainty of 0.7523. In other embodiments, NOV10B may also be localized to the microbody (peroxisome) with acertainty of 0.2291, the lysosome (lumen) with a certainty of 0.1900, or in the endoplasmic reticulum (membrane) with a certainty of 0.1000. The most likely cleavage site of the disclosed NOV10b polypeptide is between positions 25 and 26 (AAG-LG).

Table 10D. Encoded NOV10B protein sequence (SEQ ID NO:42).

MPRATALGALVSLLLLLPLPRGAGGLGERPDATADYSELDGEEGTEQQLEHYHDPCKAAV
FWGDIALDEDDLKLFHIDKARDWTKQTVGATGHSTGGLEEQASESSPDTTAMDTGTKEAG
KGSQRAIFKQAMRHWEKHTCVTFIERTDEESFIVFSYRTCGCCSYVGRRGGGPQAISIGK
NCDKFGIVAHELGHVVGFWHEHTRPDRDQHVTIIRENIQPGQEYNFLKMEAGEVSSLGET
YDFDSIMHYARNTFSRGVFLDTILPRQDDNGVRPTIGQRVRLSQGDIAQARKLYKCPGPT
CAFVSQKTSICLLHFSPTCSEGFGWQRACGETLQDTTGNFSAPGFPNGYPSYSHCVWRIS
VTPGEKIVLNFTSMDLFKSRLCWYDYVEVRDGYWRKAPLLGRFCGDKIPEPLVSTDSRLW
VEFRSSSNILGKGFFAAYEATCGGDMNKDAGQIQSPNYPDDYRPSKECVWRITVSEGFHV
GLTFQAFEIERHDSCAYDYLEVRDGPTEESALIGHFCGYEKPEDVKSSSNRLWMKFVSDG
SINKAGFAANFFKEVDECSWPDHGGCEHRCVNTLGSYKCACDPGYELAADKKMCEVACGG
FITKLNGTITSPGWPKEYPTNKNCVWQVVAPTQYRISLQFEVFELEGNDVCKYDFVEVRS
GLSPDAKLHGRFCGSETPEVITSQSNNMRVEFKSDNTVSKRGFRAHFFSDKDECAKDNGG
CQHECVNTFGSYLCRCRNGYWLHENGHDCKEAGCAHKISSVEGTLASPNWPDKYPSRREC
TWNISSTAGHRVKLTFNEFEIEQHQECAYDHLEMYDGPDSLAPILGRFCGSKKPDPTVAS

GSKCGGRLKAEVQTKELYSHAQFGDNNYPSEARCDWVIVAEDGYGVELTFRTFEVEEEAD
CGYDYMEAYDGYDSSAPRLGRFCGSGPLEEIYSAGDSLMIRFRTDDTINKKGFHARYTST
KFQDALHMKK

A search of sequence databases reveals that the NOV10B amino acid sequence has 519 of 530 amino acid residues (97%) identical to, and 519 of 530 amino acid residues (97%) similar to, the 1015 amino acid residue ptnr:SPTREMBL-ACC:Q9Y6L7 protein from Homo sapiens (Human) (TOLLOID-LIKE 2 PROTEIN).

NOV10B is expressed in at least the Parotid Salivary glands, Colon, Spinal Chord, and Lung.

The disclosed NOV10A polypeptide has homology to the amino acid sequences shown in the BLASTP data listed in Table 10E.

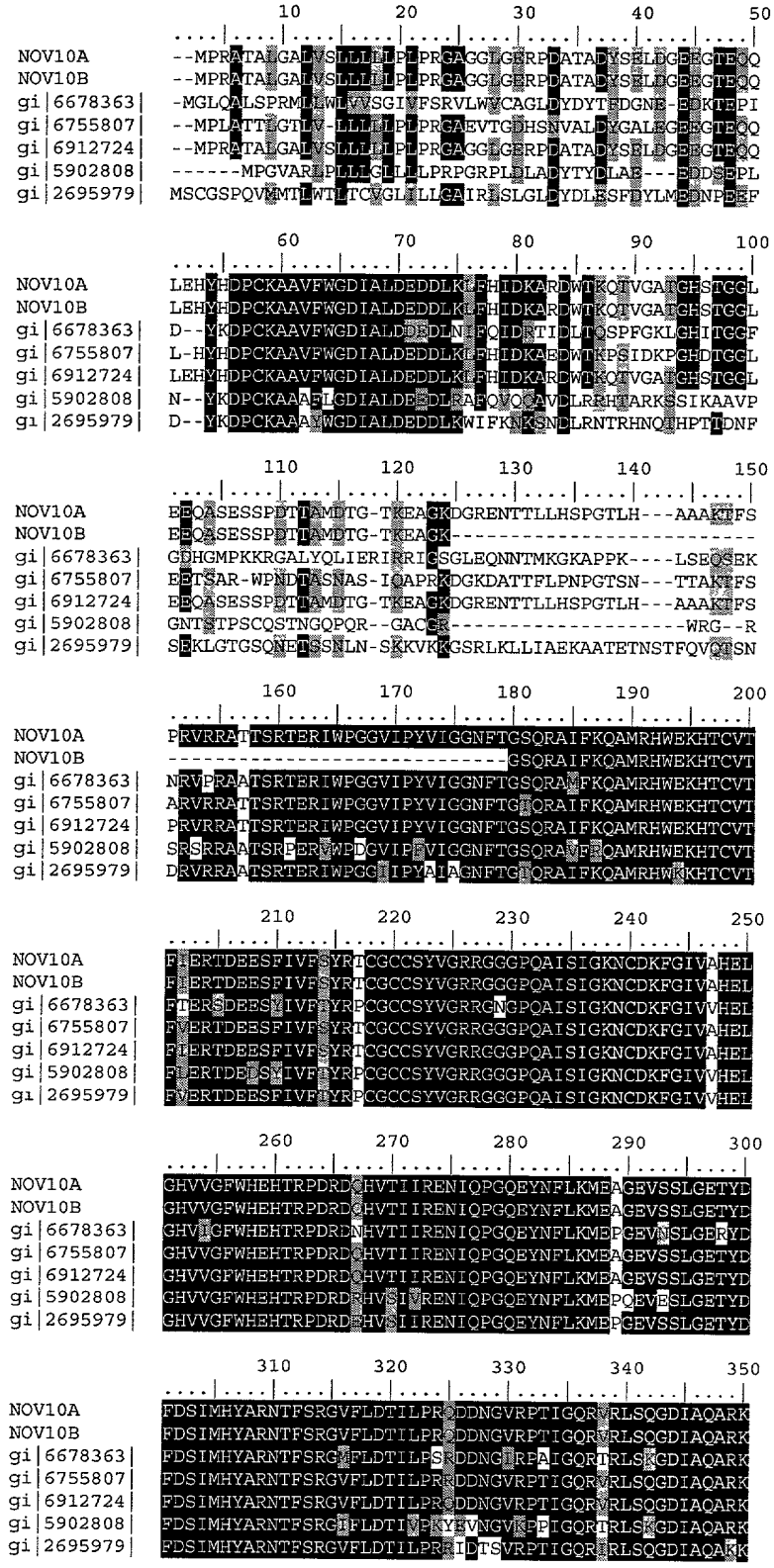
Table 10E. BLAST results for NOV10A

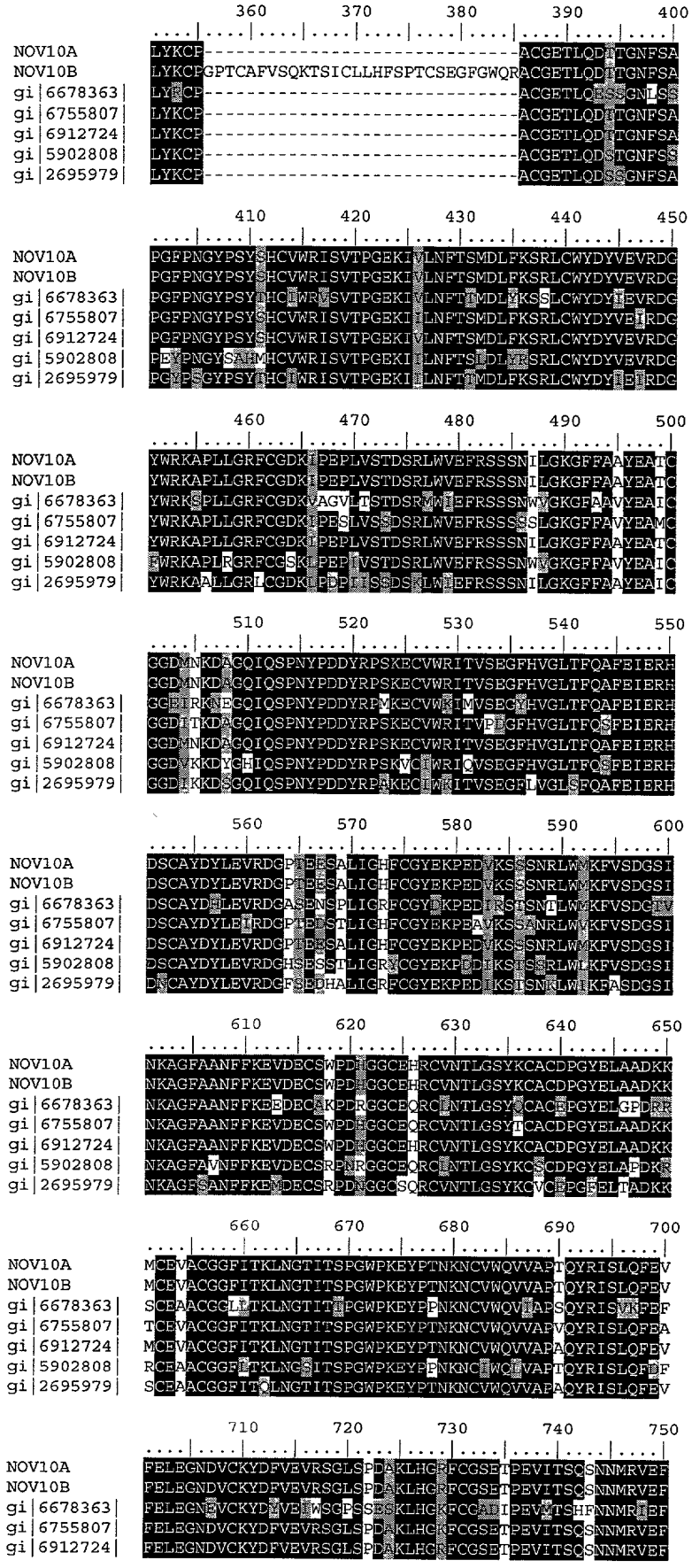
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|6678363|ref|NP_033416.1| (NM_009390)	tolloid-like [Mus musculus]	1013	70	81	0.0
gi|6755807|ref|NP_036034.1| (NM_011904)	tolloid-like 2 [Mus musculus] Length = 1012	1012	87	90	0.0
gi|6912724|ref|NP_036597.1| (NM_012465)	tolloid-like 2; KIAA0932 protein [Homo sapiens]	1015	97	97	0.0
gi|5902808|ref|NP_006119.1| (NM_006128)	bone morphogenetic protein 1, isoform 2, precursor; PCP [Homo sapiens]	823	72	81	0.0
gi|2695979|emb|CAA70854.1 (Y09661)	xolloid [Xenopus laevis]	1019	75	85	0.0

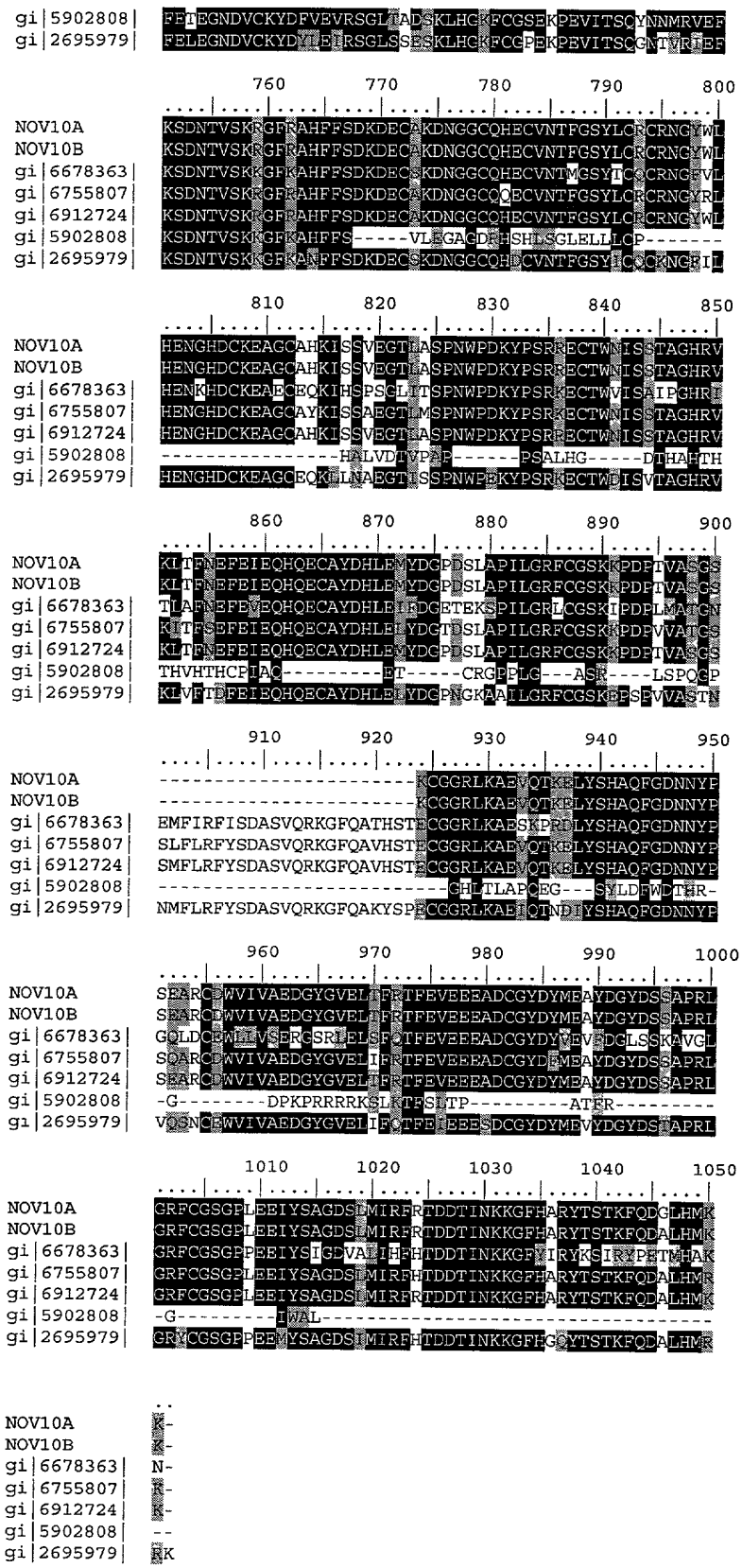
The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 10F. In the ClustalW alignment of the NOV10A protein, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties), whereas non-highlighted amino acid residues are less conserved and can potentially be altered to a much broader extent without altering protein structure or function.

Table 10F. ClustalW Analysis of NOV10A

1) Novel NOV10A (SEQ ID NO:42)
2) gi|6678363| (SEQ ID NO: 95)
3) gi|6755807| (SEQ ID NO: 96)
4) gi|6912724| (SEQ ID NO: 97)
5) gi|5902808| (SEQ ID NO: 98)
6) gi|2695979| (SEQ ID NO: 99)




NOV10A
NOV10B
gi|6678363|
gi|6755807|
gi|6912724|
gi|5902808|
gi|2695979|



Tables 10G-10I lists the domain description from DOMAIN analysis results against NOV10A. This indicates that the NOV10A sequence has properties similar to those of other proteins known to contain this domain.

Table 10G Domain Analysis of NOV10A

gnl|Pfam|pfam01400, Astacin, Astacin (Peptidase family M12A)
CD-Length = 189 residues, 100.0% aligned
Score = 280 bits (715), Expect = 4e-76

Table 10H Domain Analysis of NOV10A

gnl|Pfam|pfam00431, CUB, CUB domain
CD-Length = 110 residues, 100.0% aligned
Score = 159 bits (403), Expect = 5e-40

Table 10I Domain Analysis of NOV10A

gnl|Smart|smart00235, ZnMc, Zinc-dependent metalloprotease; Neutral zinc metallopeptidases
CD-Length = 143 residues, 99.3% aligned
Score = 130 bits (328), Expect = 3e-31

Vertebrate bone morphogenetic protein 1 (BMP-1) and Drosophila Tolloid (TLD) are prototypes of a family of metalloproteases with important roles in various developmental events. BMP-1 affects morphogenesis, at least partly, via biosynthetic processing of fibrillar collagens, while TLD affects dorsal-ventral patterning by releasing TGFbeta-like ligands from latent complexes with the secreted protein Short Gastrulation (SOG). In a screen for additional mammalian members of this family of developmental proteases, Scott et al. (*Dev Biol* 1999;213:283-300) identified novel family member mammalian Tolloid-like 2 (mTLL-2) and compare enzymatic activities and expression domains of all four known mammalian BMP-1/TLD-like proteases [BMP-1, mammalian Tolloid (mTLD), mammalian Tolloid-like 1 (mTLL-1), and mTLL-2].

Despite high sequence similarities, distinct differences are shown in ability to process fibrillar collagen precursors and to cleave Chordin, the vertebrate orthologue of SOG. As

previously demonstrated for BMP-1 and mTLD, mTLL-1 is shown to specifically process procollagen C-propeptides at the physiologically relevant site, while mTLL-2 is shown to lack this activity. BMP-1 and mTLL-1 are shown to cleave Chordin, at sites similar to procollagen C-propeptide cleavage sites, and to counteract dorsalizing effects of Chordin upon overexpression in Xenopus embryos. Proteases mTLD and mTLL-2 do not cleave Chordin. Differences in enzymatic activities and expression domains of the four proteases suggest BMP-1 as the major Chordin antagonist in early mammalian embryogenesis and in pre- and postnatal skeletogenesis.

Lysyl oxidase catalyzes the final enzymatic step required for collagen and elastin cross-linking in extracellular matrix biosynthesis. Pro-lysyl oxidase is processed by procollagen C-proteinase activity, which also removes the C-propeptides of procollagens I-III. The Bmp1 gene encodes two procollagen C-proteinases: bone morphogenetic protein 1 (BMP-1) and mammalian Tolloid (mTLD). Mammalian Tolloid-like (mTLL)-1 and -2 are two genetically distinct BMP-1-related proteinases, and mTLL-1 has been shown to have procollagen C-proteinase activity. Uzel et al. (2001) directly compared pro-lysyl oxidase processing by these four related proteinases. In vitro assays with purified recombinant enzymes show that all four proteinases productively cleave pro-lysyl oxidase at the correct physiological site but that BMP-1 is 3-, 15-, and 20-fold more efficient than mTLL-1, mTLL-2, and mTLD, respectively. To more directly assess the roles of BMP-1 and mTLL-1 in lysyl oxidase activation by connective tissue cells, fibroblasts cultured from Bmp1-null, Tll1-null, and Bmp1/Tll1 double null mouse embryos, thus lacking BMP-1/mTLD, mTLL-1, or all three enzymes, respectively, were assayed for lysyl oxidase enzyme activity and for accumulation of pro-lysyl oxidase and mature approximately 30-kDa lysyl oxidase. Wild type cells or cells singly null for Bmp1 or Tll1 all produced both pro-lysyl oxidase and processed lysyl oxidase at similar levels, indicating apparently normal levels of processing, consistent with enzyme activity data. In contrast, double null Bmp1/Tll1 cells produced predominantly unprocessed 50-kDa pro-lysyl oxidase and had lysyl oxidase enzyme activity diminished by 70% compared with wild type, Bmp1-null, and Tll1-null cells. Thus, the combination of BMP-1/mTLD and mTLL-1 is shown to be responsible for the majority of processing leading to activation of lysyl oxidase by murine embryonic fibroblasts, whereas in vitro studies identify pro-lysyl oxidase as the first known substrate for mTLL-2. (See Uzel et al. J Biol Chem 2001 Jun 22;276(25):22537-22543).

The disclosed NOV10A nucleic acid of the invention encoding a Tolloid-like 2-like protein includes the nucleic acid whose sequence is provided in Table 10A or a fragment

thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 10A while still encoding a protein that maintains its Tolloid-like 2-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 1 percent of the bases may be so changed.

The disclosed NOV10A protein of the invention includes the Tolloid-like 2-like protein whose sequence is provided in Table 10B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 10B while still encoding a protein that maintains its Tolloid-like 2-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 3 percent of the residues may be so changed.

The invention further encompasses antibodies and antibody fragments, such as F_{ab} or $(F_{ab})_2$, that bind immunospecifically to any of the proteins of the invention.

The above defined information for this invention suggests that this Tolloid-like 2-like protein (NOV10A) may function as a member of a "Tolloid-like 2-family". Therefore, the NOV10A nucleic acids and proteins identified here may be useful in potential therapeutic applications implicated in (but not limited to) various pathologies and disorders as indicated below. The potential therapeutic applications for this invention include, but are not limited to: protein therapeutic, small molecule drug target, antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), diagnostic and/or prognostic marker, gene therapy (gene delivery/gene ablation), research tools, tissue regeneration *in vivo* and *in vitro* of all tissues and cell types composing (but not limited to) those defined here.

The NOV10A nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in cancer including but not limited to various pathologies and disorders as indicated below. For example, a cDNA encoding the Tolloid-like 2-like protein (NOV10A) may be useful in gene therapy, and the Tolloid-like 2-like protein

(NOV10A) may be useful when administered to a subject in need thereof. By way of nonlimiting example, the compositions of the present invention will have efficacy for treatment of patients suffering from : xerostomia, multiple sclerosis, leukodystrophies, pain, neuroprotection, systemic lupus erythematosus, autoimmune disease, asthma, emphysema, scleroderma, allergy, ARDS, cancer, trauma, regeneration (in vitro and in vivo), viral/bacterial/parasitic infections, as well as other diseases, disorders and conditions.

. The NOV10A nucleic acid encoding the Tolloid-like 2-like protein of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV10A nucleic acids and polypeptides are further useful in the generation of antibodies that bind immuno-specifically to the novel NOV10A substances for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV10A protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV10A epitope is from about amino acids 1 to 30. In another embodiment, a NOV10A epitope is from about amino acids 300 to 330. These novel proteins can be used in assay systems for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV11

A disclosed NOV11 nucleic acid of 1604 nucleotides (also referred to as SV135004534_A) encoding a novel Cysteine sulfinic acid decarboxylase-like protein is shown in Table 11C. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 61-63 and ending with a TAG codon at nucleotides 1543-1545.

Table 11A. NOV11 nucleotide sequence (SEQ ID NO:43).

```
TAGATTATCTCTCAAACACAATTTGTTTGCTTGCTTCCAGGAGATATTGATCAACAAGAGATGATTCCAA
GTAAGAAGGGGGTTGTGCTGAATGGTGATGCAAAAGCTGGAGAAAAATTTGTTGAAGAGGCCTGTAGGCT
AATAATGGAAGAGGTGGTTTTGAAAGCTACAGATGTCAATGAGAAGGTATGTGAATGGAGGCCTCCTGAA
CAACTGAAACAGCTTCTTGATTTGGAGATGAGAGACTCAGGCGAGCCACCCCATAAACTATTGGAACTCT
GTCGGGATGTCATACACTACAGTGTCAAAACAGACCACCCAAGATTTTTCAACCAATTGTATGCTGGACT
TGATTATTACTCCTTGGTGGCCCGATTTATGACCGAAGCATTGAATCCAAGTAGTTATACGTATGAGGTG
TCCCCAGTGTTTCTGTTAGTGGAAGAAGCGGTTCTGAAGAAAATGATTGAATTTATTGGCTGGAAAGAAG
GGGATGGAATATTTAACCCAGGTGGCTCAGTGTCCAATATGTATGCAATGAATTTAGCTAGATACAAATA
TTGTCCTGATATTAAGGAAAAGGGGCTGTCTGGTTCGCCAAGATTAATCCTTTTCACATCTGCAGAGTGT
CATTACTCTATGAAGAAGGCAGCCTCTTTTCTTGGGATTGGCACTGAGAATGTTTGCTTTGTGGAAACAG
ATAGAGGTAAAATGATACCTGAGGAACTGGAGAAGCAAGTCTGGCAAGCCAGAAAAGAGGGGGCAGCACC
GTTTCTTGTCTGTGCCACTTCTGGTACAACTGTGTTGGGAGCTTTTGACCCTCTGGATGAAATAGCAGAC
ATCTGCGAGAGGCACAGCCTCTGGCTTCATGTAGATGCTTCTTGGGGTGGCTCAGCTTTGATGTCGAGGA
AGCACCGCAAGCTTCTGCATGGCATCCACAGGGCTGACTCTGTGGCCTGGAACCCACACAAGATGCTGAT
GGCTGGGATCCAGTGCTGTGCTCTCCTTGTGAAAGACAAATCTGACTTAGAAAAGAGATGCCAAGAGTTT
GTGCCTGCCTATCTCTGGCAGGAAGACAAATTTTATAATGTTGCTTTTCAGAAAAATGGTACAAAATTTA
CCCATGAAACTCAGGTGGGAAGGAATTGCAGAAGCCTGTGGTTCACCTGGAAAGCCAGGGGTGGTGAGGG
GTTGGGGTGGTTGAGGTGCCCCATGCTAGGTGATGGGAGGTACCTAGTAGATGAAATCAAGAAAAGAGAA
GGATTCAAGTTACTGATGGAACCTGAATATGCCAATATTTGCTTTTGGTACATTCCACCGAGCCTCAGAG
AGATGGAAGAAGGACCCGAGTTCTGGGCAAAACTTACACAGGTGGCCCCAGCCATTAAGGAGAGGATGAT
GAAGAAGGGAAGCTTGATGCTGGGCTACCAGCCGCACTTTACAAAGGTCAACTTCTTCCGCCAGGTGGTG
ATCAGCCCTCAAGTGAGCCGGGAGGACATGGACTTCCTCCTGGATGAGATAGACTTACTGGGTAAAGACA
TGTAGCTGTGGCTTTGGTCCCCCAGAGGCATAGATCCTATCCTGGGAGAGTTTAGATCCAGAAC
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In a search of public sequence databases, the NOV11 nucleic acid sequence, located on chromosome 3 has 985 of 1512 bases (65%) identical to a gb:GENBANK-ID:AF116547|acc:AF116547.1 mRNA from Homo sapiens (Homo sapiens cysteine sulfinic acid decarboxylase-related protein 3 (CSAD) mRNA, complete cds).

The disclosed NOV11 polypeptide (SEQ ID NO:32) encoded by SEQ ID NO:31 has 494 amino acid residues and is presented in Table 11D using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV11 has no signal peptide and is likely to be localized in the nucleus with a certainty of 0.6000. In other embodiments, NOV11 may also be localized to the microbody (peroxisome) with acertainty of 0.5720, the mitochondrial matrix space with a certainty of 0.1000, or in the lysosome (lumen) with a certainty of 0.1000.

Table 11B. Encoded NOV11 protein sequence (SEQ ID NO:44).

```
MIPSKKGVVLNGDAKAGEKFVEEACRLIMEEVVLKATDVNEKVCEWRPPEQLKQLLDLEMRDSGEPPHKL
LELCRDVIHYSVKTDHPRFFNQLYAGLDYYSLVARFMTEALNPSSYTYEVSPVFLLVEEAVLKKMIEFIG
WKEGDGIFNPGGSVSNMYAMNLARYKYCPDIKEKGLSGSPRLILFTSAECHYSMKKAASFLGIGTENVCF
VETDRGKMIPEELEKQVWQARKEGAAPFLVCATSGTTVLGAFDPLDEIADICERHSLWLHVDASWGGSAL
MSRKHRKLLHGIHRADSVAWNPHKMLMAGIQCCALLVKDKSDLEKRCQEFVPAYLWQEDKFYNVAFQKNG
TKFTHETQVGRNCRSLWFTWKARGGEGLGWLRCPMLGDGRYLVDEIKKREGFKLLMEPEYANICFWYIPP
SLREMEEGPEFWAKLTQVAPAIKERMMKKGSLMLGYQPHFTKVNFFRQVVISPQVSREDMDFLLDEIDLL
GKDM
```

A search of sequence databases reveals that the NOV11 amino acid sequence has 290 of 494 amino acid residues (58%) identical to, and 376 of 494 amino acid residues (76%)

similar to, the 493 amino acid residue ptnr:SWISSPROT-ACC:Q64611 protein from Rattus norvegicus (Rat) (CYSTEINE SULFINIC ACID DECARBOXYLASE (EC 4.1.1.29) (SULFINOALANINE DECARBOXYLASE) (CYSTEINE-SULFINATE DECARBOXYLASE)).

The disclosed NOV11 polypeptide has homology to the amino acid sequences shown in the BLASTP data listed in Table 11C.

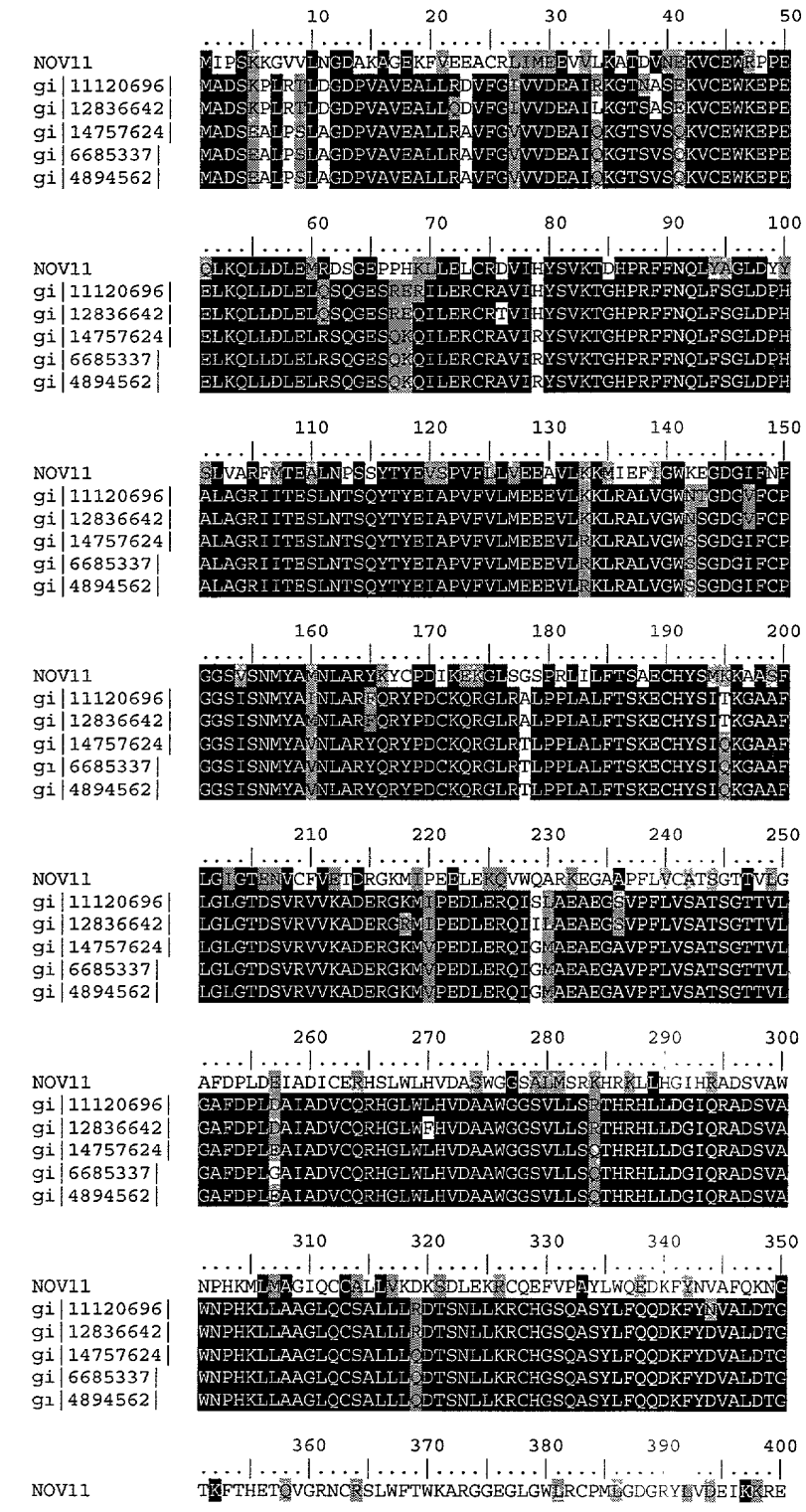
Table 11C. BLAST results for NOV11

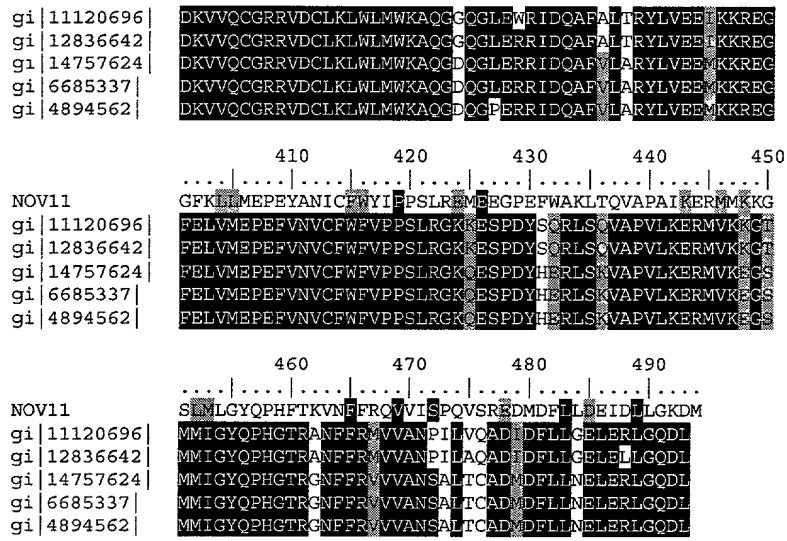
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|11120696 ref NP_068518.1 (NM_021750	cysteine-sulfinate decarboxylase [Rattus norvegicus]	493	58	75	e-175
gi|12836642 dbj BAB23747.1| (AK005015)	Putative protein/mouse	493	58	75	e-171
gi|14757624 ref XP_029712.1 (XM_029712)	hypothetical protein XP_029712 [Homo sapiens]	493	57	75	e-168
gi|6685337 sp Q9Y600 CSD_HUMAN	CYSTEINE SULFINIC ACID DECARBOXYLASE (SULFINOALANINE DECARBOXYLASE) (CYSTEINE-SULFINATE DECARBOXYLASE)	493	57	74	e-168
gi|4894562 gb AAD32546.1 AF116548 1 (AF116548)	cysteine sulfinic acid decarboxylase-related protein 4 [Homo sapiens]	493	57	75	e-167

The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 11D. In the ClustalW alignment of the NOV11 protein, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties), whereas non-highlighted amino acid residues are less conserved and can potentially be altered to a much broader extent without altering protein structure or function.

Table 11D. ClustalW Analysis of NOV11

1) Novel NOV11 (SEQ ID NO:44)
2) gi|11120696| (SEQ ID NO: 100)
3) gi|12836642| (SEQ ID NO: 101)
4) gi|14757624| (SEQ ID NO: 102)
5) gi|6685337| (SEQ ID NO: 103)
6) gi|4894562| (SEQ ID NO: 104)





Tables 1E-1F lists the domain description from DOMAIN analysis results against NOV11. This indicates that the NOV11 sequence has properties similar to those of other proteins known to contain this domain.

Table 11E Domain Analysis of NOV11

gnl|Pfam|pfam00282, pyridoxal_deC, Pyridoxal-dependent decarboxylase conserved domain.

CD-Length = 372 residues, 99.7% aligned Score = 279 bits (714), Expect = 2e-76

Table 11F Domain Analysis of NOV11

gnl|Pfam|pfam00266, aminotran_5, Aminotransferase class-V
CD-Length = 354 residues Score = 42.7 bits (99), Expect = 5e-05

Cysteine sulfinic acid decarboxylase (CSAD), the rate-limiting enzyme in taurine biosynthesis, was found to be activated under conditions that favor protein phosphorylation and inactivated under conditions favoring protein dephosphorylation. Direct incorporation of 32P into purified CSAD has been demonstrated with [gamma 32P]ATP and PKC, but not PKA. In addition, the 32P labeling of CSAD was inhibited by PKC inhibitors suggesting that PKC is responsible for phosphorylation of CSAD in the brain. Okadaic acid had no effect on CSAD activity at 10 microM suggesting that protein phosphatase-2C (PrP-2C) might be involved in the dephosphorylation of CSAD. Furthermore, it was found that either glutamate- or high K(+)-induced depolarization increased CSAD activity as well as 32P-incorporation

into CSAD in neuronal cultures, supporting the notion that the CSAD activity is endogenously regulated by protein phosphorylation in the brain. A model to link neuronal excitation, phosphorylation of CSAD and increase in taurine biosynthesis is proposed.

Met metabolism occurs primarily by activation of Met to AdoMet and further metabolism of AdoMet by either the transmethylation-transsulfuration pathway or the polyamine biosynthetic pathway. The catabolism of the methyl group and sulfur atom of Met ultimately appears to be dependent upon the transmethylation-transsulfuration pathway because the MTA formed as the co-product of polyamine synthesis is efficiently recycled to Met. On the other hand, the fate of the four-carbon chain of Met appears to depend upon the initial fate of the Met molecule. During transsulfuration, the carbon chain is released as alpha-ketobutyrate, which is further metabolized to CO2. In the polyamine pathway, the carboxyl carbon of Met is lost in the formation of dAdoMet, whereas the other three carbons are ultimately excreted as polyamine derivatives and degradation products. The role of the transamination pathway of Met metabolism is not firmly established. Cys (which may be formed from the sulfur of Met and the carbons of serine via the transsulfuration pathway) appears to be converted to taurine and CO2 primarily by the cysteinesulfinate pathway, and to sulfate and pyruvate primarily by desulfuration pathways in which a reduced form of sulfur with a relatively long biological half-life appears to be an intermediate. With the exception of the nitrogen of Met that is incorporated into polyamines, the nitrogen of Met or Cys is incorporated into urea after it is released as ammonium [in the reactions catalyzed by cystathionase with either cystathionine (from Met) or cystine (from Cys) as substrate] or it is transferred to a keto acid (in Cys or Met transamination). Many areas of sulfur-containing amino acid metabolism need further study. The magnitude of AdoMet flux through the polyamine pathway in the intact animal as well as details about the reactions involved in this pathway remain to be determined. Both the pathways and the possible physiological role of alternate (AdoMet-independent) Met metabolism, including the transamination pathway, must be elucidated. Despite the growing interest in taurine, investigation of Cys metabolism has been a relatively inactive area during the past two decades. Apparent discrepancies in the reported data on Cys metabolism need to be resolved. Future work should consider the role of extrahepatic tissues in amino acid metabolism as well as species differences in the relative roles of various pathways in the metabolism of Met and Cys.

Both immunocytochemical and electrophysiological methods have been employed to determine whether the localization of the taurine synthetic enzyme, cysteine sulfinic acid decarboxylase, (CSAD) and the postsynaptic action of taurine in the CA1 region of rat

hippocampus are consistent with the hypothesis that taurine may be used as a neurotransmitter by some hippocampal neurons. At the light microscopic level, CSAD-immunoreactivity (CSAD-IR) was found in the pyramidal basket cells, and around pyramidal cells in stratum pyramidale and stratum radiatum. At the electron microscopic level, CSAD-IR was seen most often in the soma and the dendrites and was rather infrequent in the axon or the nerve terminals. Electrophysiological observations on the in vitro hippocampal slice demonstrated that pyramidal neurons respond to artificially applied taurine with inhibition that depended in large part upon an increased chloride conductance. Although electrophysiological observations are consistent with a neurotransmitter role for taurine, results from immunocytochemical studies suggest a minor role for taurine as a neurotransmitter. In fact, immunocytochemical observations suggested that taurine may be used as a neurotransmitter only by a small number of pyramidal basket interneurons, the vast majority of CSAD-positive neurons may use taurine for other functions.

The effect of 3-acetylpyridine (3-AP) administration on the biosynthesis of taurine in the rat brain has been studied. Treatment with 3-AP induced a significant decrease in the cerebellar contents of taurine and its metabolic precursors, cysteine sulfinic acid (CSA) and cysteic acid (CA), as well as a selective degeneration of climbing fibers in the molecular layer of the cerebellum. It was found that the activity of cerebral cysteine dioxygenase, the enzyme catalyzing the formation of CSA from cysteine, consisted of two systems with low and high Km values. The 3-AP-induced attenuation of cysteine dioxygenase activity with a low Km value was noted only in the cerebellum, while that with a high Km value was detected not only in the cerebellum but also in other brain areas such as the medulla oblongata, striatum and cerebral cortex. In contrast, no alteration in the activity of cysteine sulfinic acid decarboxylase (CSD) was observed in any brain areas examined following the administration of 3-AP. Furthermore, it was found that essentially no cystamine as well as a very low activity of cysteamine dioxygenase is present in the brain. The present results suggest that taurine in the brain is synthesized from cysteine, mainly by the CSA and CA pathways, and the observed decline of cerebellar taurine in 3-AP-treated rats may be due to an attenuation of the biosynthesis, possibly at the step of cysteine dioxygenase. A possible regulatory role of cysteine dioxygenase with a low Km value in the biosynthesis of cerebral taurine is also suggested.

The activity of cysteinesulfinic acid decarboxylase (CSAD, EC 4.1.1.29) in extracts of liver of seven mammals varied greatly, whereas in extracts of brain from the same species, the variation was less marked. CSAD activity was readily measured in extracts of spinal cord from

the same species, except those from rhesus monkey and man. The most noteworthy observation was the complete absence of CSAD activity in extracts of optic nerves and of sciatic nerves from all seven mammals. This suggests that taurine biosynthesis does not occur within axons and that intraaxonal taurine is supplied by axonal transport from the cell body.

Taurine, cysteinesulfinic acid decarboxylase (CSAD), glutamate, gamma-aminobutyric acid (GABA), and glutamic acid decarboxylase (GAD) were measured in subcellular fractions prepared from occipital lobe of fetal and neonatal rhesus monkeys. In addition, the distribution of [35S]taurine in subcellular fractions was determined after administration to the fetus via the mother, to the neonate via administration to the mother prior to birth, and directly to the neonate at various times after birth. CSAD, glutamate, GABA, and GAD all were found to be low or unmeasurable in early fetal life and to increase during late fetal and early neonatal life to reach values found in the mother. Taurine was present in large amounts in early fetal life and decreased slowly during neonatal life, arriving at amounts found in the mother not until after 150 days of age. Significant amounts of taurine, CSAD, GABA, and GAD were associated with nerve ending components with some indication that the proportion of brain taurine found in these organelles increases during development. All subcellular pools of taurine were rapidly labeled by exogenously administered [35S]taurine. The subcellular distribution of all the components measured was compatible with the neurotransmitter or putative neurotransmitter functions of glutamate, GABA, and taurine. The large amount of these three amino acids exceeds that required for such function. The excess of glutamate and GABA may be used as a source of energy. The function of the excess of taurine is still not clear, although circumstantial evidence favors an important role in the development and maturation of the CNS.

The disclosed NOV11 nucleic acid of the invention encoding a Cysteine sulfinic acid decarboxylase -like protein includes the nucleic acid whose sequence is provided in Table 11A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 11A while still encoding a protein that maintains its Cysteine sulfinic acid decarboxylase-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones

are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 35 percent of the bases may be so changed.

The disclosed NOV11 protein of the invention includes the Cysteine sulfinic acid decarboxylase-like protein whose sequence is provided in Table 11B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 11B while still encoding a protein that maintains its Cysteine sulfinic acid decarboxylase -like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 42 percent of the residues may be so changed.

The invention further encompasses antibodies and antibody fragments, such as F_{ab} or $(F_{ab})_2$, that bind immunospecifically to any of the proteins of the invention.

The above defined information for this invention suggests that this Cysteine sulfinic acid decarboxylase-like protein (NOV11) may function as a member of a "Cysteine sulfinic acid decarboxylase family". Therefore, the NOV11 nucleic acids and proteins identified here may be useful in potential therapeutic applications implicated in (but not limited to) various pathologies and disorders as indicated below. The potential therapeutic applications for this invention include, but are not limited to: protein therapeutic, small molecule drug target, antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), diagnostic and/or prognostic marker, gene therapy (gene delivery/gene ablation), research tools, tissue regeneration *in vivo* and *in vitro* of all tissues and cell types composing (but not limited to) those defined here.

The NOV11 nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in cancer including but not limited to various pathologies and disorders as indicated below. For example, a cDNA encoding the Cysteine sulfinic acid decarboxylase-like protein (NOV11) may be useful in gene therapy, and the Cysteine sulfinic acid decarboxylase -like protein (NOV11) may be useful when administered to a subject in need thereof. By way of nonlimiting example, the compositions of the present invention will have efficacy for treatment of patients suffering from Adrenoleukodystrophy , Congenital Adrenal Hyperplasia, Diabetes,Von Hippel-Lindau (VHL) syndrome , Pancreatitis, Obesity, Hyperparathyroidism, Hypoparathyroidism, Fertility, cancers such as those occurring in pancreas, bone, colon, brain, lung, breast, or prostate. Endometriosis, Xerostomia

Scleroderma Hypercalceimia, Ulcers Von Hippel-Lindau (VHL) syndrome, Cirrhosis,Transplantation, Inflammatory bowel disease, Diverticular disease, Hirschsprung's disease , Crohn's Disease, Appendicitis Osteoporosis, Hypercalceimia, Arthritis, Ankylosing spondylitis, Scoliosis Arthritis, Tendinitis on Hippel-Lindau (VHL) syndrome , Alzheimer's disease, Stroke, Tuberous sclerosis, hypercalceimia, Parkinson's disease, Huntington's disease, Cerebral palsy, Epilepsy, Lesch-Nyhan syndrome, Multiple sclerosis,Ataxia-telangiectasia, Leukodystrophies, Behavioral disorders, Addiction, Anxiety, Pain, Endocrine dysfunctions, Diabetes, obesity, Growth and reproductive disorders Multiple sclerosis, Leukodystrophies, Pain, Myasthenia gravis, Pain, Systemic lupus erythematosus , Autoimmune disease, Asthma, Emphysema, Scleroderma, allergy, ARDS, Psoriasis, Actinic keratosis ,Tuberous sclerosis, Acne, Hair growth, allopecia, pigmentation disorders, Renal artery stenosis, Interstitial nephritis, Glomerulonephritis, Polycystic kidney disease, Systemic lupus erythematosus, Renal tubular acidosis, IgA nephropathy, Hypercalceimia, Lesch-Nyhan syndrome and other diseases, disorders and conditions of the like. The NOV11 nucleic acid encoding the Cysteine sulfinic acid decarboxylase-like protein of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV11 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immuno-specifically to the novel NOV11 substances for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV11 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV11 epitope is from about amino acids 25 to 50. In another embodiment, a NOV11 epitope is from about amino acids 100 to 140. In additional embodiments, a NOV11 epitope is from about amino acids 140 to 170, from about amino acids 235 to 260, and from about amino acids 300 to 320. These novel proteins can be used in assay systems for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOVX Nucleic Acids and Polypeptides

One aspect of the invention pertains to isolated nucleic acid molecules that encode NOVX polypeptides or biologically active portions thereof. Also included in the invention are nucleic acid fragments sufficient for use as hybridization probes to identify NOVX-encoding

nucleic acids (*e.g.*, NOVX mRNAs) and fragments for use as PCR primers for the amplification and/or mutation of NOVX nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA), RNA molecules (*e.g.*, mRNA), analogs of the DNA or RNA generated using nucleotide analogs, and derivatives, fragments and homologs thereof. The nucleic acid molecule may be single-stranded or double-stranded, but preferably is comprised double-stranded DNA.

An NOVX nucleic acid can encode a mature NOVX polypeptide. As used herein, a "mature" form of a polypeptide or protein disclosed in the present invention is the product of a naturally occurring polypeptide or precursor form or proprotein. The naturally occurring polypeptide, precursor or proprotein includes, by way of nonlimiting example, the full-length gene product, encoded by the corresponding gene. Alternatively, it may be defined as the polypeptide, precursor or proprotein encoded by an ORF described herein. The product "mature" form arises, again by way of nonlimiting example, as a result of one or more naturally occurring processing steps as they may take place within the cell, or host cell, in which the gene product arises. Examples of such processing steps leading to a "mature" form of a polypeptide or protein include the cleavage of the N-terminal methionine residue encoded by the initiation codon of an ORF, or the proteolytic cleavage of a signal peptide or leader sequence. Thus a mature form arising from a precursor polypeptide or protein that has residues 1 to N, where residue 1 is the N-terminal methionine, would have residues 2 through N remaining after removal of the N-terminal methionine. Alternatively, a mature form arising from a precursor polypeptide or protein having residues 1 to N, in which an N-terminal signal sequence from residue 1 to residue M is cleaved, would have the residues from residue M+1 to residue N remaining. Further as used herein, a "mature" form of a polypeptide or protein may arise from a step of post-translational modification other than a proteolytic cleavage event. Such additional processes include, by way of non-limiting example, glycosylation, myristoylation or phosphorylation. In general, a mature polypeptide or protein may result from the operation of only one of these processes, or a combination of any of them.

The term "probes", as utilized herein, refers to nucleic acid sequences of variable length, preferably between at least about 10 nucleotides (nt), 100 nt, or as many as approximately, *e.g.*, 6,000 nt, depending upon the specific use. Probes are used in the detection of identical, similar, or complementary nucleic acid sequences. Longer length probes are generally obtained from a natural or recombinant source, are highly specific, and much slower to hybridize than shorter-length oligomer probes. Probes may be single- or

double-stranded and designed to have specificity in PCR, membrane-based hybridization technologies, or ELISA-like technologies.

The term "isolated" nucleic acid molecule, as utilized herein, is one, which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid. Preferably, an "isolated" nucleic acid is free of sequences which naturally flank the nucleic acid (*i.e.*, sequences located at the 5'- and 3'-termini of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated NOVX nucleic acid molecules can contain less than about 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell/tissue from which the nucleic acid is derived (*e.g.*, brain, heart, liver, spleen, etc.). Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material or culture medium when produced by recombinant techniques, or of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the invention, *e.g.*, a nucleic acid molecule having the nucleotide sequence SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, or a complement of this aforementioned nucleotide sequence, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or a portion of the nucleic acid sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43 as a hybridization probe, NOVX molecules can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook, *et al.*, (eds.), MOLECULAR CLONING: A LABORATORY MANUAL 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989; and Ausubel, *et al.*, (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, NY, 1993.)

A nucleic acid of the invention can be amplified using cDNA, mRNA or alternatively, genomic DNA, as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, oligonucleotides corresponding to NOVX nucleotide sequences can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

As used herein, the term "oligonucleotide" refers to a series of linked nucleotide residues, which oligonucleotide has a sufficient number of nucleotide bases to be used in a PCR reaction. A short oligonucleotide sequence may be based on, or designed from, a

genomic or cDNA sequence and is used to amplify, confirm, or reveal the presence of an identical, similar or complementary DNA or RNA in a particular cell or tissue. Oligonucleotides comprise portions of a nucleic acid sequence having about 10 nt, 50 nt, or 100 nt in length, preferably about 15 nt to 30 nt in length. In one embodiment of the invention, an oligonucleotide comprising a nucleic acid molecule less than 100 nt in length would further comprise at least 6 contiguous nucleotides SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, or a complement thereof. Oligonucleotides may be chemically synthesized and may also be used as probes.

In another embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule that is a complement of the nucleotide sequence shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, or a portion of this nucleotide sequence (*e.g.*, a fragment that can be used as a probe or primer or a fragment encoding a biologically-active portion of an NOVX polypeptide). A nucleic acid molecule that is complementary to the nucleotide sequence shown SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 or 43 is one that is sufficiently complementary to the nucleotide sequence shown SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 or 43 that it can hydrogen bond with little or no mismatches to the nucleotide sequence shown SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, thereby forming a stable duplex.

As used herein, the term "complementary" refers to Watson-Crick or Hoogsteen base pairing between nucleotides units of a nucleic acid molecule, and the term "binding" means the physical or chemical interaction between two polypeptides or compounds or associated polypeptides or compounds or combinations thereof. Binding includes ionic, non-ionic, van der Waals, hydrophobic interactions, and the like. A physical interaction can be either direct or indirect. Indirect interactions may be through or due to the effects of another polypeptide or compound. Direct binding refers to interactions that do not take place through, or due to, the effect of another polypeptide or compound, but instead are without other substantial chemical intermediates.

Fragments provided herein are defined as sequences of at least 6 (contiguous) nucleic acids or at least 4 (contiguous) amino acids, a length sufficient to allow for specific hybridization in the case of nucleic acids or for specific recognition of an epitope in the case of amino acids, respectively, and are at most some portion less than a full length sequence. Fragments may be derived from any contiguous portion of a nucleic acid or amino acid sequence of choice. Derivatives are nucleic acid sequences or amino acid sequences formed

from the native compounds either directly or by modification or partial substitution. Analogs are nucleic acid sequences or amino acid sequences that have a structure similar to, but not identical to, the native compound but differs from it in respect to certain components or side chains. Analogs may be synthetic or from a different evolutionary origin and may have a similar or opposite metabolic activity compared to wild type. Homologs are nucleic acid sequences or amino acid sequences of a particular gene that are derived from different species.

Derivatives and analogs may be full length or other than full length, if the derivative or analog contains a modified nucleic acid or amino acid, as described below. Derivatives or analogs of the nucleic acids or proteins of the invention include, but are not limited to, molecules comprising regions that are substantially homologous to the nucleic acids or proteins of the invention, in various embodiments, by at least about 70%, 80%, or 95% identity (with a preferred identity of 80-95%) over a nucleic acid or amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art, or whose encoding nucleic acid is capable of hybridizing to the complement of a sequence encoding the aforementioned proteins under stringent, moderately stringent, or low stringent conditions. *See e.g.* Ausubel, *et al.*, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, NY, 1993, and below.

A "homologous nucleic acid sequence" or "homologous amino acid sequence," or variations thereof, refer to sequences characterized by a homology at the nucleotide level or amino acid level as discussed above. Homologous nucleotide sequences encode those sequences coding for isoforms of NOVX polypeptides. Isoforms can be expressed in different tissues of the same organism as a result of, for example, alternative splicing of RNA. Alternatively, isoforms can be encoded by different genes. In the invention, homologous nucleotide sequences include nucleotide sequences encoding for an NOVX polypeptide of species other than humans, including, but not limited to: vertebrates, and thus can include, *e.g.*, frog, mouse, rat, rabbit, dog, cat cow, horse, and other organisms. Homologous nucleotide sequences also include, but are not limited to, naturally occurring allelic variations and mutations of the nucleotide sequences set forth herein. A homologous nucleotide sequence does not, however, include the exact nucleotide sequence encoding human NOVX protein. Homologous nucleic acid sequences include those nucleic acid sequences that encode conservative amino acid substitutions (see below) in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, as well as a polypeptide possessing NOVX biological activity. Various biological activities of the NOVX proteins are described below.

An NOVX polypeptide is encoded by the open reading frame ("ORF") of an NOVX nucleic acid. An ORF corresponds to a nucleotide sequence that could potentially be translated into a polypeptide. A stretch of nucleic acids comprising an ORF is uninterrupted by a stop codon. An ORF that represents the coding sequence for a full protein begins with an ATG "start" codon and terminates with one of the three "stop" codons, namely, TAA, TAG, or TGA. For the purposes of this invention, an ORF may be any part of a coding sequence, with or without a start codon, a stop codon, or both. For an ORF to be considered as a good candidate for coding for a *bona fide* cellular protein, a minimum size requirement is often set, *e.g.,* a stretch of DNA that would encode a protein of 50 amino acids or more.

The nucleotide sequences determined from the cloning of the human NOVX genes allows for the generation of probes and primers designed for use in identifying and/or cloning NOVX homologues in other cell types, *e.g.* from other tissues, as well as NOVX homologues from other vertebrates. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, 25, 50, 100, 150, 200, 250, 300, 350 or 400 consecutive sense strand nucleotide sequence SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 or 43; or an anti-sense strand nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 or 43; or of a naturally occurring mutant of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43.

Probes based on the human NOVX nucleotide sequences can be used to detect transcripts or genomic sequences encoding the same or homologous proteins. In various embodiments, the probe further comprises a label group attached thereto, *e.g.* the label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or tissues which mis-express an NOVX protein, such as by measuring a level of an NOVX-encoding nucleic acid in a sample of cells from a subject *e.g.*, detecting NOVX mRNA levels or determining whether a genomic NOVX gene has been mutated or deleted.

"A polypeptide having a biologically-active portion of an NOVX polypeptide" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. A nucleic acid fragment encoding a "biologically-active portion of NOVX" can be prepared by isolating a portion SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 or 43, that encodes a polypeptide

having an NOVX biological activity (the biological activities of the NOVX proteins are described below), expressing the encoded portion of NOVX protein (*e.g.*, by recombinant expression *in vitro*) and assessing the activity of the encoded portion of NOVX.

NOVX Nucleic Acid and Polypeptide Variants

The invention further encompasses nucleic acid molecules that differ from the nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43 due to degeneracy of the genetic code and thus encode the same NOVX proteins as that encoded by the nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43. In another embodiment, an isolated nucleic acid molecule of the invention has a nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44.

In addition to the human NOVX nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of the NOVX polypeptides may exist within a population (*e.g.*, the human population). Such genetic polymorphism in the NOVX genes may exist among individuals within a population due to natural allelic variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame (ORF) encoding an NOVX protein, preferably a vertebrate NOVX protein. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of the NOVX genes. Any and all such nucleotide variations and resulting amino acid polymorphisms in the NOVX polypeptides, which are the result of natural allelic variation and that do not alter the functional activity of the NOVX polypeptides, are intended to be within the scope of the invention.

Moreover, nucleic acid molecules encoding NOVX proteins from other species, and thus that have a nucleotide sequence that differs from the human SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43 are intended to be within the scope of the invention. Nucleic acid molecules corresponding to natural allelic variants and homologues of the NOVX cDNAs of the invention can be isolated based on their homology to the human NOVX nucleic acids disclosed herein using the human cDNAs, or a portion thereof, as a hybridization probe according to standard hybridization techniques under stringent hybridization conditions.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 6 nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43. In another embodiment, the nucleic acid is at least 10, 25, 50, 100, 250, 500, 750, 1000, 1500, or 2000 or more nucleotides in length. In yet another embodiment, an isolated nucleic acid molecule of the invention hybridizes to the coding region. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% homologous to each other typically remain hybridized to each other.

Homologs (*i.e.,* nucleic acids encoding NOVX proteins derived from species other than human) or other related sequences (*e.g.,* paralogs) can be obtained by low, moderate or high stringency hybridization with all or a portion of the particular human sequence as a probe using methods well known in the art for nucleic acid hybridization and cloning.

As used herein, the phrase "stringent hybridization conditions" refers to conditions under which a probe, primer or oligonucleotide will hybridize to its target sequence, but to no other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures than shorter sequences. Generally, stringent conditions are selected to be about 5 °C lower than the thermal melting point (Tm) for the specific sequence at a defined ionic strength and pH. The Tm is the temperature (under defined ionic strength, pH and nucleic acid concentration) at which 50% of the probes complementary to the target sequence hybridize to the target sequence at equilibrium. Since the target sequences are generally present at excess, at Tm, 50% of the probes are occupied at equilibrium. Typically, stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion (or other salts) at

pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes, primers or oligonucleotides (*e.g.,* 10 nt to 50 nt) and at least about 60°C for longer probes, primers and oligonucleotides. Stringent conditions may also be achieved with the addition of destabilizing agents, such as formamide.

Stringent conditions are known to those skilled in the art and can be found in Ausubel, *et al.*, (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Preferably, the conditions are such that sequences at least about 65%, 70%, 75%, 85%, 90%, 95%, 98%, or 99% homologous to each other typically remain

hybridized to each other. A non-limiting example of stringent hybridization conditions are hybridization in a high salt buffer comprising 6X SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 mg/ml denatured salmon sperm DNA at 65°C, followed by one or more washes in 0.2X SSC, 0.01% BSA at 50°C. An isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to the sequences SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, corresponds to a naturally-occurring nucleic acid molecule. As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (*e.g.*, encodes a natural protein).

In a second embodiment, a nucleic acid sequence that is hybridizable to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, or fragments, analogs or derivatives thereof, under conditions of moderate stringency is provided. A non-limiting example of moderate stringency hybridization conditions are hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 mg/ml denatured salmon sperm DNA at 55°C, followed by one or more washes in 1X SSC, 0.1% SDS at 37°C. Other conditions of moderate stringency that may be used are well-known within the art. *See, e.g.*, Ausubel, et *al.* (eds.), 1993, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, NY, and Kriegler, 1990; GENE TRANSFER AND EXPRESSION, A LABORATORY MANUAL, Stockton Press, NY.

In a third embodiment, a nucleic acid that is hybridizable to the nucleic acid molecule comprising the nucleotide sequences SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, or fragments, analogs or derivatives thereof, under conditions of low stringency, is provided. A non-limiting example of low stringency hybridization conditions are hybridization in 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 mg/ml denatured salmon sperm DNA, 10% (wt/vol) dextran sulfate at 40°C, followed by one or more washes in 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS at 50°C. Other conditions of low stringency that may be used are well known in the art (*e.g.*, as employed for cross-species hybridizations). *See, e.g.,* Ausubel, *et al.* (eds.), 1993, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, NY, and Kriegler, 1990, GENE TRANSFER AND EXPRESSION, A LABORATORY MANUAL, Stockton Press, NY; Shilo and Weinberg, 1981. *Proc Natl Acad Sci USA* **78**: 6789-6792.

Conservative Mutations

In addition to naturally-occurring allelic variants of NOVX sequences that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequences SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, thereby leading to changes in the amino acid sequences of the encoded NOVX proteins, without altering the functional ability of said NOVX proteins. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in the sequence SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequences of the NOVX proteins without altering their biological activity, whereas an "essential" amino acid residue is required for such biological activity. For example, amino acid residues that are conserved among the NOVX proteins of the invention are predicted to be particularly non-amenable to alteration. Amino acids for which conservative substitutions can be made are well-known within the art.

Another aspect of the invention pertains to nucleic acid molecules encoding NOVX proteins that contain changes in amino acid residues that are not essential for activity. Such NOVX proteins differ in amino acid sequence from SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43 yet retain biological activity. In one embodiment, the isolated nucleic acid molecule comprises a nucleotide sequence encoding a protein, wherein the protein comprises an amino acid sequence at least about 45% homologous to the amino acid sequences SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 and 44. Preferably, the protein encoded by the nucleic acid molecule is at least about 60% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 and 44; more preferably at least about 70% homologous SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44; still more preferably at least about 80% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44; even more preferably at least about 90% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44; and most preferably at least about 95% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44.

An isolated nucleic acid molecule encoding an NOVX protein homologous to the protein of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44 can be created by introducing one or more nucleotide substitutions, additions or

deletions into the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein.

Mutations can be introduced into SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43 by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted, non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined within the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted non-essential amino acid residue in the NOVX protein is replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of an NOVX coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for NOVX biological activity to identify mutants that retain activity. Following mutagenesis SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, the encoded protein can be expressed by any recombinant technology known in the art and the activity of the protein can be determined.

The relatedness of amino acid families may also be determined based on side chain interactions. Substituted amino acids may be fully conserved "strong" residues or fully conserved "weak" residues. The "strong" group of conserved amino acid residues may be any one of the following groups: STA, NEQK, NHQK, NDEQ, QHRK, MILV, MILF, HY, FYW, wherein the single letter amino acid codes are grouped by those amino acids that may be substituted for each other. Likewise, the "weak" group of conserved residues may be any one of the following: CSA, ATV, SAG, STNK, STPA, SGND, SNDEQK, NDEQHK, NEQHRK, VLIM, HFY, wherein the letters within each group represent the single letter amino acid code.

In one embodiment, a mutant NOVX protein can be assayed for (*i*) the ability to form protein:protein interactions with other NOVX proteins, other cell-surface proteins, or biologically-active portions thereof, (*ii*) complex formation between a mutant NOVX protein

and an NOVX ligand; or (*iii*) the ability of a mutant NOVX protein to bind to an intracellular target protein or biologically-active portion thereof; (*e.g.* avidin proteins).

In yet another embodiment, a mutant NOVX protein can be assayed for the ability to regulate a specific biological function (*e.g.*, regulation of insulin release).

Antisense Nucleic Acids

Another aspect of the invention pertains to isolated antisense nucleic acid molecules that are hybridizable to or complementary to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, or fragments, analogs or derivatives thereof. An "antisense" nucleic acid comprises a nucleotide sequence that is complementary to a "sense" nucleic acid encoding a protein (*e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence). In specific aspects, antisense nucleic acid molecules are provided that comprise a sequence complementary to at least about 10, 25, 50, 100, 250 or 500 nucleotides or an entire NOVX coding strand, or to only a portion thereof. Nucleic acid molecules encoding fragments, homologs, derivatives and analogs of an NOVX protein of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44, or antisense nucleic acids complementary to an NOVX nucleic acid sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, are additionally provided.

In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence encoding an NOVX protein. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence encoding the NOVX protein. The term "noncoding region" refers to 5' and 3' sequences which flank the coding region that are not translated into amino acids (*i.e.*, also referred to as 5' and 3' untranslated regions).

Given the coding strand sequences encoding the NOVX protein disclosed herein, antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick or Hoogsteen base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of NOVX mRNA, but more preferably is an oligonucleotide that is antisense to only a portion of the coding or noncoding region of NOVX mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation

start site of NOVX mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis or enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally-occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids (*e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used).

Examples of modified nucleotides that can be used to generate the antisense nucleic acid include: 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding an NOVX protein to thereby inhibit expression of the protein (*e.g.*, by inhibiting transcription and/or translation). The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule that binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified

such that they specifically bind to receptors or antigens expressed on a selected cell surface (*e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies that bind to cell surface receptors or antigens). The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient nucleic acid molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

In yet another embodiment, the antisense nucleic acid molecule of the invention is an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other. *See, e.g.,* Gaultier, *et al.*, 1987. *Nucl. Acids Res.* **15**: 6625-6641. The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (*See, e.g.,* Inoue, *et al.* 1987. *Nucl. Acids Res.* **15**: 6131-6148) or a chimeric RNA-DNA analogue (*See, e.g.,* Inoue, *et al.*, 1987. *FEBS Lett.* **215**: 327-330.

Ribozymes and PNA Moieties

Nucleic acid modifications include, by way of non-limiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject.

In one embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity that are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes as described in Haselhoff and Gerlach 1988. *Nature* 334: 585-591) can be used to catalytically cleave NOVX mRNA transcripts to thereby inhibit translation of NOVX mRNA. A ribozyme having specificity for an NOVX-encoding nucleic acid can be designed based upon the nucleotide sequence of an NOVX cDNA disclosed herein (*i.e.*, SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in an NOVX-encoding mRNA. *See, e.g.*, U.S. Patent 4,987,071 to Cech, *et al.* and U.S. Patent 5,116,742 to Cech, *et al.* NOVX mRNA can also be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. *See, e.g.*, Bartel *et al.*, (1993) *Science* 261:1411-1418.

Alternatively, NOVX gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the NOVX nucleic acid (*e.g.*, the NOVX promoter and/or enhancers) to form triple helical structures that prevent transcription of the NOVX gene in target cells. *See, e.g.,* Helene, 1991. *Anticancer Drug Des.* 6: 569-84; Helene, *et al.* 1992. *Ann. N.Y. Acad. Sci.* 660: 27-36; Maher, 1992. *Bioassays* 14: 807-15.

In various embodiments, the NOVX nucleic acids can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids. *See, e.g.,* Hyrup, *et al.*, 1996. *Bioorg Med Chem* 4: 5-23. As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics (*e.g.*, DNA mimics) in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup, *et al.*, 1996. *supra*; Perry-O'Keefe, *et al.*, 1996. *Proc. Natl. Acad. Sci. USA* 93: 14670-14675.

PNAs of NOVX can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, *e.g.*, inducing transcription or translation arrest or inhibiting replication. PNAs of NOVX can also be used, for example, in the analysis of single base pair mutations in a gene (*e.g.*, PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, *e.g.*, S_1 nucleases (*See,* Hyrup, *et al.,* 1996.*supra*); or as probes or primers for DNA sequence and hybridization (*See,* Hyrup, *et al.*, 1996, *supra*; Perry-O'Keefe, *et al.,* 1996. *supra*).

In another embodiment, PNAs of NOVX can be modified, *e.g.*, to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras of NOVX can be generated that may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes (*e.g.*, RNase H and DNA polymerases) to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (*see,* Hyrup, et al., 1996. *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup, *et al.,* 1996.

supra and Finn, *et al.*, 1996. *Nucl Acids Res* 24: 3357-3363. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry, and modified nucleoside analogs, *e.g.*, 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite, can be used between the PNA and the 5' end of DNA. *See, e.g.,* Mag, *et al.*, 1989. *Nucl Acid Res* 17: 5973-5988. PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment. *See, e.g.,* Finn, *et al.*, 1996. *supra.* Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment. *See, e.g.,* Petersen, *et al.*, 1975. *Bioorg. Med. Chem. Lett.* 5: 1119-11124.

In other embodiments, the oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (*see, e.g.*, Letsinger, *et al.*, 1989. *Proc. Natl. Acad. Sci. U.S.A.* 86: 6553-6556; Lemaitre, *et al.*, 1987. *Proc. Natl. Acad. Sci.* 84: 648-652; PCT Publication No. WO88/09810) or the blood-brain barrier (*see, e.g.*, PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization triggered cleavage agents (*see, e.g.,* Krol, *et al.*, 1988. *BioTechniques* 6:958-976) or intercalating agents (*see, e.g.*, Zon, 1988. *Pharm. Res.* 5: 539-549). To this end, the oligonucleotide may be conjugated to another molecule, *e.g.*, a peptide, a hybridization triggered cross-linking agent, a transport agent, a hybridization-triggered cleavage agent, and the like.

NOVX Polypeptides

A polypeptide according to the invention includes a polypeptide including the amino acid sequence of NOVX polypeptides whose sequences are provided in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residues shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44 while still encoding a protein that maintains its NOVX activities and physiological functions, or a functional fragment thereof.

In general, an NOVX variant that preserves NOVX-like function includes any variant in which residues at a particular position in the sequence have been substituted by other amino acids, and further include the possibility of inserting an additional residue or residues between two residues of the parent protein as well as the possibility of deleting one or more residues from the parent sequence. Any amino acid substitution, insertion, or deletion is encompassed

by the invention. In favorable circumstances, the substitution is a conservative substitution as defined above.

One aspect of the invention pertains to isolated NOVX proteins, and biologically-active portions thereof, or derivatives, fragments, analogs or homologs thereof. Also provided are polypeptide fragments suitable for use as immunogens to raise anti-NOVX antibodies. In one embodiment, native NOVX proteins can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, NOVX proteins are produced by recombinant DNA techniques. Alternative to recombinant expression, an NOVX protein or polypeptide can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" polypeptide or protein or biologically-active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the NOVX protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of NOVX proteins in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly-produced. In one embodiment, the language "substantially free of cellular material" includes preparations of NOVX proteins having less than about 30% (by dry weight) of non-NOVX proteins (also referred to herein as a "contaminating protein"), more preferably less than about 20% of non-NOVX proteins, still more preferably less than about 10% of non-NOVX proteins, and most preferably less than about 5% of non-NOVX proteins. When the NOVX protein or biologically-active portion thereof is recombinantly-produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, more preferably less than about 10%, and most preferably less than about 5% of the volume of the NOVX protein preparation.

The language "substantially free of chemical precursors or other chemicals" includes preparations of NOVX proteins in which the protein is separated from chemical precursors or other chemicals that are involved in the synthesis of the protein. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of NOVX proteins having less than about 30% (by dry weight) of chemical precursors or non-NOVX chemicals, more preferably less than about 20% chemical precursors or non-NOVX chemicals, still more preferably less than about 10% chemical precursors or non-NOVX chemicals, and most preferably less than about 5% chemical precursors or non-NOVX chemicals.

Biologically-active portions of NOVX proteins include peptides comprising amino acid sequences sufficiently homologous to or derived from the amino acid sequences of the NOVX proteins (*e.g.*, the amino acid sequence shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44) that include fewer amino acids than the full-length NOVX proteins, and exhibit at least one activity of an NOVX protein. Typically, biologically-active portions comprise a domain or motif with at least one activity of the NOVX protein. A biologically-active portion of an NOVX protein can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acid residues in length.

Moreover, other biologically-active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of a native NOVX protein.

In an embodiment, the NOVX protein has an amino acid sequence shown SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44. In other embodiments, the NOVX protein is substantially homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44, and retains the functional activity of the protein of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44, yet differs in amino acid sequence due to natural allelic variation or mutagenesis, as described in detail, below. Accordingly, in another embodiment, the NOVX protein is a protein that comprises an amino acid sequence at least about 45% homologous to the amino acid sequence SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44, and retains the functional activity of the NOVX proteins of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44.

Determining Homology Between Two or More Sequences

To determine the percent homology of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are homologous at that position (*i.e.*, as used herein amino acid or nucleic acid "homology" is equivalent to amino acid or nucleic acid "identity").

The nucleic acid sequence homology may be determined as the degree of identity between two sequences. The homology may be determined using computer programs known in the art, such as GAP software provided in the GCG program package. *See,* Needleman and Wunsch, 1970. *J Mol Biol* 48: 443-453. Using GCG GAP software with the following settings for nucleic acid sequence comparison: GAP creation penalty of 5.0 and GAP extension penalty of 0.3, the coding region of the analogous nucleic acid sequences referred to above exhibits a degree of identity preferably of at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, with the CDS (encoding) part of the DNA sequence shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43.

The term "sequence identity" refers to the degree to which two polynucleotide or polypeptide sequences are identical on a residue-by-residue basis over a particular region of comparison. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over that region of comparison, determining the number of positions at which the identical nucleic acid base (*e.g.,* A, T, C, G, U, or I, in the case of nucleic acids) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the region of comparison (*i.e.,* the window size), and multiplying the result by 100 to yield the percentage of sequence identity. The term "substantial identity" as used herein denotes a characteristic of a polynucleotide sequence, wherein the polynucleotide comprises a sequence that has at least 80 percent sequence identity, preferably at least 85 percent identity and often 90 to 95 percent sequence identity, more usually at least 99 percent sequence identity as compared to a reference sequence over a comparison region.

Chimeric and Fusion Proteins

The invention also provides NOVX chimeric or fusion proteins. As used herein, an NOVX "chimeric protein" or "fusion protein" comprises an NOVX polypeptide operatively-linked to a non-NOVX polypeptide. An "NOVX polypeptide" refers to a polypeptide having an amino acid sequence corresponding to an NOVX protein SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 26, 28, 40, 42 or 44, whereas a "non-NOVX polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein that is not substantially homologous to the NOVX protein, *e.g.,* a protein that is different from the NOVX protein and that is derived from the same or a different organism. Within an NOVX fusion protein the NOVX polypeptide can correspond to all or a portion of an NOVX protein. In one embodiment, an NOVX fusion protein comprises at least one biologically-

active portion of an NOVX protein. In another embodiment, an NOVX fusion protein comprises at least two biologically-active portions of an NOVX protein. In yet another embodiment, an NOVX fusion protein comprises at least three biologically-active portions of an NOVX protein. Within the fusion protein, the term "operatively-linked" is intended to indicate that the NOVX polypeptide and the non-NOVX polypeptide are fused in-frame with one another. The non-NOVX polypeptide can be fused to the N-terminus or C-terminus of the NOVX polypeptide.

In one embodiment, the fusion protein is a GST-NOVX fusion protein in which the NOVX sequences are fused to the C-terminus of the GST (glutathione S-transferase) sequences. Such fusion proteins can facilitate the purification of recombinant NOVX polypeptides.

In another embodiment, the fusion protein is an NOVX protein containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of NOVX can be increased through use of a heterologous signal sequence.

In yet another embodiment, the fusion protein is an NOVX-immunoglobulin fusion protein in which the NOVX sequences are fused to sequences derived from a member of the immunoglobulin protein family. The NOVX-immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between an NOVX ligand and an NOVX protein on the surface of a cell, to thereby suppress NOVX-mediated signal transduction *in vivo*. The NOVX-immunoglobulin fusion proteins can be used to affect the bioavailability of an NOVX cognate ligand. Inhibition of the NOVX ligand/NOVX interaction may be useful therapeutically for both the treatment of proliferative and differentiative disorders, as well as modulating (*e.g.* promoting or inhibiting) cell survival. Moreover, the NOVX-immunoglobulin fusion proteins of the invention can be used as immunogens to produce anti-NOVX antibodies in a subject, to purify NOVX ligands, and in screening assays to identify molecules that inhibit the interaction of NOVX with an NOVX ligand.

An NOVX chimeric or fusion protein of the invention can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, *e.g.*, by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In

another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive gene fragments that can subsequently be annealed and reamplified to generate a chimeric gene sequence (*see, e.g.,* Ausubel, *et al.* (eds.) CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). An NOVX-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the NOVX protein.

NOVX Agonists and Antagonists

The invention also pertains to variants of the NOVX proteins that function as either NOVX agonists (*i.e.,* mimetics) or as NOVX antagonists. Variants of the NOVX protein can be generated by mutagenesis (*e.g.*, discrete point mutation or truncation of the NOVX protein). An agonist of the NOVX protein can retain substantially the same, or a subset of, the biological activities of the naturally occurring form of the NOVX protein. An antagonist of the NOVX protein can inhibit one or more of the activities of the naturally occurring form of the NOVX protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the NOVX protein. Thus, specific biological effects can be elicited by treatment with a variant of limited function. In one embodiment, treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein has fewer side effects in a subject relative to treatment with the naturally occurring form of the NOVX proteins.

Variants of the NOVX proteins that function as either NOVX agonists (*i.e.,* mimetics) or as NOVX antagonists can be identified by screening combinatorial libraries of mutants (*e.g.*, truncation mutants) of the NOVX proteins for NOVX protein agonist or antagonist activity. In one embodiment, a variegated library of NOVX variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of NOVX variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential NOVX sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display) containing the set of NOVX sequences therein. There are a variety of methods which can be used to produce libraries of potential NOVX variants from a degenerate oligonucleotide sequence. Chemical

synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential NOVX sequences. Methods for synthesizing degenerate oligonucleotides are well-known within the art. *See, e.g.,* Narang, 1983. *Tetrahedron* 39: 3; Itakura, *et al.*, 1984. *Annu. Rev. Biochem.* 53: 323; Itakura, *et al.*, 1984. *Science* 198: 1056; Ike, *et al.*, 1983. *Nucl. Acids Res.* 11: 477.

Polypeptide Libraries

In addition, libraries of fragments of the NOVX protein coding sequences can be used to generate a variegated population of NOVX fragments for screening and subsequent selection of variants of an NOVX protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of an NOVX coding sequence with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double-stranded DNA that can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S_1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, expression libraries can be derived which encodes N-terminal and internal fragments of various sizes of the NOVX proteins.

Various techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of NOVX proteins. The most widely used techniques, which are amenable to high throughput analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a new technique that enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify NOVX variants. *See, e.g.,* Arkin and Yourvan, 1992. *Proc. Natl. Acad. Sci. USA* 89: 7811-7815; Delgrave, *et al.*, 1993. *Protein Engineering* 6:327-331.

Anti-NOVX Antibodies

Also included in the invention are antibodies to NOVX proteins, or fragments of NOVX proteins. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin (Ig) molecules, i.e., molecules that contain an antigen binding site that specifically binds (immunoreacts with) an antigen. Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, F_{ab}, $F_{ab'}$ and $F_{(ab')2}$ fragments, and an F_{ab} expression library. In general, an antibody molecule obtained from humans relates to any of the classes IgG, IgM, IgA, IgE and IgD, which differ from one another by the nature of the heavy chain present in the molecule. Certain classes have subclasses as well, such as IgG_1, IgG_2, and others. Furthermore, in humans, the light chain may be a kappa chain or a lambda chain. Reference herein to antibodies includes a reference to all such classes, subclasses and types of human antibody species.

An isolated NOVX-related protein of the invention may be intended to serve as an antigen, or a portion or fragment thereof, and additionally can be used as an immunogen to generate antibodies that immunospecifically bind the antigen, using standard techniques for polyclonal and monoclonal antibody preparation. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments of the antigen for use as immunogens. An antigenic peptide fragment comprises at least 6 amino acid residues of the amino acid sequence of the full length protein and encompasses an epitope thereof such that an antibody raised against the peptide forms a specific immune complex with the full length protein or with any fragment that contains the epitope. Preferably, the antigenic peptide comprises at least 10 amino acid residues, or at least 15 amino acid residues, or at least 20 amino acid residues, or at least 30 amino acid residues. Preferred epitopes encompassed by the antigenic peptide are regions of the protein that are located on its surface; commonly these are hydrophilic regions.

In certain embodiments of the invention, at least one epitope encompassed by the antigenic peptide is a region of NOVX-related protein that is located on the surface of the protein, *e.g.*, a hydrophilic region. A hydrophobicity analysis of the human NOVX-related protein sequence will indicate which regions of a NOVX-related protein are particularly hydrophilic and, therefore, are likely to encode surface residues useful for targeting antibody production. As a means for targeting antibody production, hydropathy plots showing regions of hydrophilicity and hydrophobicity may be generated by any method well known in the art, including, for example, the Kyte Doolittle or the Hopp Woods methods, either with or without Fourier transformation. See, *e.g.*, Hopp and Woods, 1981, *Proc. Nat. Acad. Sci. USA* 78:

3824-3828; Kyte and Doolittle 1982, *J. Mol. Biol.* 157: 105-142, each of which is incorporated herein by reference in its entirety. Antibodies that are specific for one or more domains within an antigenic protein, or derivatives, fragments, analogs or homologs thereof, are also provided herein.

A protein of the invention, or a derivative, fragment, analog, homolog or ortholog thereof, may be utilized as an immunogen in the generation of antibodies that immunospecifically bind these protein components.

Various procedures known within the art may be used for the production of polyclonal or monoclonal antibodies directed against a protein of the invention, or against derivatives, fragments, analogs homologs or orthologs thereof (see, for example, Antibodies: A Laboratory Manual, Harlow and Lane, 1988, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, incorporated herein by reference). Some of these antibodies are discussed below.

Polyclonal Antibodies

For the production of polyclonal antibodies, various suitable host animals (e.g., rabbit, goat, mouse or other mammal) may be immunized by one or more injections with the native protein, a synthetic variant thereof, or a derivative of the foregoing. An appropriate immunogenic preparation can contain, for example, the naturally occurring immunogenic protein, a chemically synthesized polypeptide representing the immunogenic protein, or a recombinantly expressed immunogenic protein. Furthermore, the protein may be conjugated to a second protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. The preparation can further include an adjuvant. Various adjuvants used to increase the immunological response include, but are not limited to, Freund's (complete and incomplete), mineral gels (e.g., aluminum hydroxide), surface active substances (e.g., lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, dinitrophenol, etc.), adjuvants usable in humans such as Bacille Calmette-Guerin and Corynebacterium parvum, or similar immunostimulatory agents. Additional examples of adjuvants which can be employed include MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate).

The polyclonal antibody molecules directed against the immunogenic protein can be isolated from the mammal (e.g., from the blood) and further purified by well known techniques, such as affinity chromatography using protein A or protein G, which provide primarily the IgG fraction of immune serum. Subsequently, or alternatively, the specific

antigen which is the target of the immunoglobulin sought, or an epitope thereof, may be immobilized on a column to purify the immune specific antibody by immunoaffinity chromatography. Purification of immunoglobulins is discussed, for example, by D. Wilkinson (The Scientist, published by The Scientist, Inc., Philadelphia PA, Vol. 14, No. 8 (April 17, 2000), pp. 25-28).

Monoclonal Antibodies

The term "monoclonal antibody" (MAb) or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one molecular species of antibody molecule consisting of a unique light chain gene product and a unique heavy chain gene product. In particular, the complementarity determining regions (CDRs) of the monoclonal antibody are identical in all the molecules of the population. MAbs thus contain an antigen binding site capable of immunoreacting with a particular epitope of the antigen characterized by a unique binding affinity for it.

Monoclonal antibodies can be prepared using hybridoma methods, such as those described by Kohler and Milstein, *Nature*, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes can be immunized in vitro.

The immunizing agent will typically include the protein antigen, a fragment thereof or a fusion protein thereof. Generally, either peripheral blood lymphocytes are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, MONOCLONAL ANTIBODIES: PRINCIPLES AND PRACTICE, Academic Press, (1986) pp. 59-103). Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells can be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, *J. Immunol.*, 133:3001 (1984); Brodeur et al., MONOCLONAL ANTIBODY PRODUCTION TECHNIQUES AND APPLICATIONS, Marcel Dekker, Inc., New York, (1987) pp. 51-63).

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, *Anal. Biochem.*, 107:220 (1980). Preferably, antibodies having a high degree of specificity and a high binding affinity for the target antigen are isolated.

After the desired hybridoma cells are identified, the clones can be subcloned by limiting dilution procedures and grown by standard methods. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells can be grown in vivo as ascites in a mammal.

The monoclonal antibodies secreted by the subclones can be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies can also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to

obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also can be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison, *Nature* 368, 812-13 (1994)) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

Humanized Antibodies

The antibodies directed against the protein antigens of the invention can further comprise humanized antibodies or human antibodies. These antibodies are suitable for administration to humans without engendering an immune response by the human against the administered immunoglobulin. Humanized forms of antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) that are principally comprised of the sequence of a human immunoglobulin, and contain minimal sequence derived from a non-human immunoglobulin. Humanization can be performed following the method of Winter and co-workers (Jones et al., *Nature*, 321:522-525 (1986); Riechmann et al., *Nature*, 332:323-327 (1988); Verhoeyen et al., *Science*, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. (See also U.S. Patent No. 5,225,539.) In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies can also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin (Jones et al., 1986; Riechmann et al., 1988; and Presta, *Curr. Op. Struct. Biol.*, 2:593-596 (1992)).

Human Antibodies

Fully human antibodies relate to antibody molecules in which essentially the entire sequences of both the light chain and the heavy chain, including the CDRs, arise from human genes. Such antibodies are termed "human antibodies", or "fully human antibodies" herein. Human monoclonal antibodies can be prepared by the trioma technique; the human B-cell hybridoma technique (see Kozbor, et al., 1983 Immunol Today 4: 72) and the EBV hybridoma technique to produce human monoclonal antibodies (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies may be utilized in the practice of the present invention and may be produced by using human hybridomas (see Cote, et al., 1983. Proc Natl Acad Sci USA 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus in vitro (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96).

In addition, human antibodies can also be produced using additional techniques, including phage display libraries (Hoogenboom and Winter, *J. Mol. Biol.*, 227:381 (1991); Marks et al., *J. Mol. Biol.*, 222:581 (1991)). Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in Marks et al. (*Bio/Technology* 10, 779-783 (1992)); Lonberg et al. (*Nature* 368 856-859 (1994)); Morrison (*Nature* 368, 812-13 (1994)); Fishwild et al,(*Nature Biotechnology* 14, 845-51 (1996)); Neuberger (*Nature Biotechnology* 14, 826 (1996)); and Lonberg and Huszar (*Intern. Rev. Immunol.* 13 65-93 (1995)).

Human antibodies may additionally be produced using transgenic nonhuman animals which are modified so as to produce fully human antibodies rather than the animal's endogenous antibodies in response to challenge by an antigen. (See PCT publication WO94/02602). The endogenous genes encoding the heavy and light immunoglobulin chains in the nonhuman host have been incapacitated, and active loci encoding human heavy and light chain immunoglobulins are inserted into the host's genome. The human genes are incorporated, for example, using yeast artificial chromosomes containing the requisite human DNA segments. An animal which provides all the desired modifications is then obtained as progeny by crossbreeding intermediate transgenic animals containing fewer than the full

complement of the modifications. The preferred embodiment of such a nonhuman animal is a mouse, and is termed the Xenomouse™ as disclosed in PCT publications WO 96/33735 and WO 96/34096. This animal produces B cells which secrete fully human immunoglobulins. The antibodies can be obtained directly from the animal after immunization with an immunogen of interest, as, for example, a preparation of a polyclonal antibody, or alternatively from immortalized B cells derived from the animal, such as hybridomas producing monoclonal antibodies. Additionally, the genes encoding the immunoglobulins with human variable regions can be recovered and expressed to obtain the antibodies directly, or can be further modified to obtain analogs of antibodies such as, for example, single chain Fv molecules.

An example of a method of producing a nonhuman host, exemplified as a mouse, lacking expression of an endogenous immunoglobulin heavy chain is disclosed in U.S. Patent No. 5,939,598. It can be obtained by a method including deleting the J segment genes from at least one endogenous heavy chain locus in an embryonic stem cell to prevent rearrangement of the locus and to prevent formation of a transcript of a rearranged immunoglobulin heavy chain locus, the deletion being effected by a targeting vector containing a gene encoding a selectable marker; and producing from the embryonic stem cell a transgenic mouse whose somatic and germ cells contain the gene encoding the selectable marker.

A method for producing an antibody of interest, such as a human antibody, is disclosed in U.S. Patent No. 5,916,771. It includes introducing an expression vector that contains a nucleotide sequence encoding a heavy chain into one mammalian host cell in culture, introducing an expression vector containing a nucleotide sequence encoding a light chain into another mammalian host cell, and fusing the two cells to form a hybrid cell. The hybrid cell expresses an antibody containing the heavy chain and the light chain.

In a further improvement on this procedure, a method for identifying a clinically relevant epitope on an immunogen, and a correlative method for selecting an antibody that binds immunospecifically to the relevant epitope with high affinity, are disclosed in PCT publication WO 99/53049.

F_{ab} Fragments and Single Chain Antibodies

According to the invention, techniques can be adapted for the production of single-chain antibodies specific to an antigenic protein of the invention (see e.g., U.S. Patent No. 4,946,778). In addition, methods can be adapted for the construction of F_{ab} expression libraries (see e.g., Huse, et al., 1989 Science 246: 1275-1281) to allow rapid and effective

identification of monoclonal F_{ab} fragments with the desired specificity for a protein or derivatives, fragments, analogs or homologs thereof. Antibody fragments that contain the idiotypes to a protein antigen may be produced by techniques known in the art including, but not limited to: (i) an $F_{(ab')2}$ fragment produced by pepsin digestion of an antibody molecule; (ii) an F_{ab} fragment generated by reducing the disulfide bridges of an $F_{(ab')2}$ fragment; (iii) an F_{ab} fragment generated by the treatment of the antibody molecule with papain and a reducing agent and (iv) F_v fragments.

Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for an antigenic protein of the invention. The second binding target is any other antigen, and advantageously is a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, *Nature*, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker *et al.*, 1991 *EMBO J.*, 10:3655-3659.

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., *Methods in Enzymology*, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part

of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. $F(ab')_2$ bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., *Science* 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate $F(ab')_2$ fragments. These fragments are reduced in the presence of the dithiol comRho-Interacting Proteing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Additionally, Fab' fragments can be directly recovered from E. coli and chemically coupled to form bispecific antibodies. Shalaby et al., *J. Exp. Med.* 175:217-225 (1992) describe the production of a fully humanized bispecific antibody $F(ab')_2$ molecule. Each Fab' fragment was separately secreted from E. coli and subjected to directed chemical coupling in vitro to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., *J. Immunol.* 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al., *Proc. Natl. Acad. Sci. USA* 90:6444-6448 (1993) has

provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber et al., *J. Immunol.* 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., *J. Immunol.* 147:60 (1991).

Exemplary bispecific antibodies can bind to two different epitopes, at least one of which originates in the protein antigen of the invention. Alternatively, an anti-antigenic arm of an immunoglobulin molecule can be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular antigen. Bispecific antibodies can also be used to direct cytotoxic agents to cells which express a particular antigen. These antibodies possess an antigen-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the protein antigen described herein and further binds tissue factor (TF).

Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360; WO 92/200373; EP 03089). It is contemplated that the antibodies can be prepared in vitro using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins can be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

Effector Function Engineering

It can be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, e.g., the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) can be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated can have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et al., J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity can also be prepared using heterobifunctional cross-linkers as described in Wolff et al. Cancer Research, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and can thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al., Anti-Cancer Drug Design, 3: 219-230 (1989).

Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas aeruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ^{212}Bi, ^{131}I, ^{131}In, ^{90}Y, and ^{186}Re.

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates

(such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., Science, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

In another embodiment, the antibody can be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g., avidin) that is in turn conjugated to a cytotoxic agent.

In one embodiment, methods for the screening of antibodies that possess the desired specificity include, but are not limited to, enzyme-linked immunosorbent assay (ELISA) and other immunologically-mediated techniques known within the art. In a specific embodiment, selection of antibodies that are specific to a particular domain of an NOVX protein is facilitated by generation of hybridomas that bind to the fragment of an NOVX protein possessing such a domain. Thus, antibodies that are specific for a desired domain within an NOVX protein, or derivatives, fragments, analogs or homologs thereof, are also provided herein.

Anti-NOVX antibodies may be used in methods known within the art relating to the localization and/or quantitation of an NOVX protein (*e.g.,* for use in measuring levels of the NOVX protein within appropriate physiological samples, for use in diagnostic methods, for use in imaging the protein, and the like). In a given embodiment, antibodies for NOVX proteins, or derivatives, fragments, analogs or homologs thereof, that contain the antibody derived binding domain, are utilized as pharmacologically-active compounds (hereinafter "Therapeutics").

An anti-NOVX antibody (*e.g.*, monoclonal antibody) can be used to isolate an NOVX polypeptide by standard techniques, such as affinity chromatography or immunoprecipitation. An anti-NOVX antibody can facilitate the purification of natural NOVX polypeptide from cells and of recombinantly-produced NOVX polypeptide expressed in host cells. Moreover, an anti-NOVX antibody can be used to detect NOVX protein (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the NOVX protein. Anti-NOVX antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the

antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

NOVX Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding an NOVX protein, or derivatives, fragments, analogs or homologs thereof. As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively-linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, that is operatively-linked to the nucleic acid

sequence to be expressed. Within a recombinant expression vector, "operably-linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner that allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell).

The term "regulatory sequence" is intended to includes promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cell and those that direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (*e.g.*, NOVX proteins, mutant forms of NOVX proteins, fusion proteins, etc.).

The recombinant expression vectors of the invention can be designed for expression of NOVX proteins in prokaryotic or eukaryotic cells. For example, NOVX proteins can be expressed in bacterial cells such as *Escherichia coli*, insect cells (using baculovirus expression vectors) yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *Escherichia coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: (*i*) to increase expression of recombinant protein; (*ii*) to increase the solubility of the recombinant protein; and (*iii*) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition

sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988. *Gene* 67: 31-40), pMAL (New England Biolabs, Beverly, Mass.) and pRIT5 (Pharmacia, Piscataway, N.J.) that fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amrann *et al.*, (1988) *Gene* 69:301-315) and pET 11d (Studier *et al.*, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 60-89).

One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein. *See, e.g.,* Gottesman, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 119-128. Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (*see, e.g.,* Wada, *et al.*, 1992. *Nucl. Acids Res.* 20: 2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the NOVX expression vector is a yeast expression vector. Examples of vectors for expression in yeast *Saccharomyces cerivisae* include pYepSec1 (Baldari, *et al.*, 1987. *EMBO J.* 6: 229-234), pMFa (Kurjan and Herskowitz, 1982. *Cell* 30: 933-943), pJRY88 (Schultz *et al.*, 1987. *Gene* 54: 113-123), pYES2 (Invitrogen Corporation, San Diego, Calif.), and picZ (InVitrogen Corp, San Diego, Calif.).

Alternatively, NOVX can be expressed in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (*e.g.*, SF9 cells) include the pAc series (Smith, *et al.*, 1983. *Mol. Cell. Biol.* 3: 2156-2165) and the pVL series (Lucklow and Summers, 1989. *Virology* 170: 31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987. *Nature* 329: 840) and pMT2PC (Kaufman, *et al.*, 1987. *EMBO J.* 6: 187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, adenovirus 2, cytomegalovirus, and simian virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see, *e.g.*, Chapters 16 and 17 of

Sambrook, *et al.*, MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert, *et al.*, 1987. *Genes Dev.* 1: 268-277), lymphoid-specific promoters (Calame and Eaton, 1988. *Adv. Immunol.* 43: 235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989. *EMBO J.* 8: 729-733) and immunoglobulins (Banerji, *et al.*, 1983. *Cell* 33: 729-740; Queen and Baltimore, 1983. *Cell* 33: 741-748), neuron-specific promoters (*e.g.*, the neurofilament promoter; Byrne and Ruddle, 1989. *Proc. Natl. Acad. Sci. USA* 86: 5473-5477), pancreas-specific promoters (Edlund, *et al.*, 1985. *Science* 230: 912-916), and mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Pat. No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, *e.g.*, the murine hox promoters (Kessel and Gruss, 1990. *Science* 249: 374-379) and the α-fetoprotein promoter (Campes and Tilghman, 1989. *Genes Dev.* 3: 537-546).

The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively-linked to a regulatory sequence in a manner that allows for expression (by transcription of the DNA molecule) of an RNA molecule that is antisense to NOVX mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the antisense orientation can be chosen that direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen that direct constitutive, tissue specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes *see, e.g.,* Weintraub, *et al.*, "Antisense RNA as a molecular tool for genetic analysis," *Reviews-Trends in Genetics*, Vol. 1(1) 1986.

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer

not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, NOVX protein can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Various selectable markers include those that confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be introduced into a host cell on the same vector as that encoding NOVX or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) NOVX protein. Accordingly, the invention further provides methods for producing NOVX protein using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding NOVX protein has been introduced) in a suitable medium such that NOVX protein is produced. In another embodiment, the method further comprises isolating NOVX protein from the medium or the host cell.

Transgenic NOVX Animals

The host cells of the invention can also be used to produce non-human transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which NOVX protein-coding sequences have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous NOVX sequences have been introduced into their genome or homologous recombinant animals in which endogenous NOVX sequences have been altered. Such animals are useful for studying the function and/or activity of NOVX protein and for identifying and/or evaluating modulators of NOVX protein activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA that is integrated into the genome of a cell from which a transgenic animal develops and that remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous NOVX gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing NOVX-encoding nucleic acid into the male pronuclei of a fertilized oocyte (*e.g.*, by microinjection, retroviral infection) and allowing the oocyte to develop in a pseudopregnant female foster animal. The human NOVX cDNA sequences SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43 can be introduced as a transgene into the genome of a non-human animal. Alternatively, a non-human homologue of the human NOVX gene, such as a mouse NOVX gene, can be isolated based on hybridization to the human NOVX cDNA (described further *supra*) and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably-linked to the NOVX transgene to direct expression of NOVX protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866; 4,870,009; and 4,873,191; and Hogan, 1986. In: MANIPULATING THE MOUSE

EMBRYO, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the NOVX transgene in its genome and/or expression of NOVX mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene-encoding NOVX protein can further be bred to other transgenic animals carrying other transgenes.

To create a homologous recombinant animal, a vector is prepared which contains at least a portion of an NOVX gene into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the NOVX gene. The NOVX gene can be a human gene (*e.g.*, the cDNA of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43), but more preferably, is a non-human homologue of a human NOVX gene. For example, a mouse homologue of human NOVX gene of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43 can be used to construct a homologous recombination vector suitable for altering an endogenous NOVX gene in the mouse genome. In one embodiment, the vector is designed such that, upon homologous recombination, the endogenous NOVX gene is functionally disrupted (*i.e.*, no longer encodes a functional protein; also referred to as a "knock out" vector).

Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous NOVX gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous NOVX protein). In the homologous recombination vector, the altered portion of the NOVX gene is flanked at its 5'- and 3'-termini by additional nucleic acid of the NOVX gene to allow for homologous recombination to occur between the exogenous NOVX gene carried by the vector and an endogenous NOVX gene in an embryonic stem cell. The additional flanking NOVX nucleic acid is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5'- and 3'-termini) are included in the vector. *See, e.g.,* Thomas, *et al.*, 1987. *Cell* 51: 503 for a description of homologous recombination vectors. The vector is ten introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced NOVX gene has homologously-recombined with the endogenous NOVX gene are selected. *See, e.g.*, Li, *et al.*, 1992. *Cell* 69: 915.

The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras. *See, e.g.*, Bradley, 1987. In: TERATOCARCINOMAS AND

EMBRYONIC STEM CELLS: A PRACTICAL APPROACH, Robertson, ed. IRL, Oxford, pp. 113-152. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously-recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously-recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, 1991. *Curr. Opin. Biotechnol.* 2: 823-829; PCT International Publication Nos.: WO 90/11354; WO 91/01140; WO 92/0968; and WO 93/04169.

In another embodiment, transgenic non-humans animals can be produced that contain selected systems that allow for regulated expression of the transgene. One example of such a system is the cre/loxP recombinase system of bacteriophage P1. For a description of the cre/loxP recombinase system, *See, e.g.*, Lakso, *et al.*, 1992. *Proc. Natl. Acad. Sci. USA* 89: 6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae. See,* O'Gorman, *et al.*, 1991. *Science* 251:1351-1355. If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, *e.g.*, by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, *et al.*, 1997. *Nature* 385: 810-813. In brief, a cell (*e.g.*, a somatic cell) from the transgenic animal can be isolated and induced to exit the growth cycle and enter G_0 phase. The quiescent cell can then be fused, *e.g.*, through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyte and then transferred to pseudopregnant female foster animal. The offspring borne of this female foster animal will be a clone of the animal from which the cell (*e.g.*, the somatic cell) is isolated.

Pharmaceutical Compositions

The NOVX nucleic acid molecules, NOVX proteins, and anti-NOVX antibodies (also referred to herein as "active compounds") of the invention, and derivatives, fragments, analogs and homologs thereof, can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or

antibody and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, finger's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (*i.e.,* topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol,

propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (*e.g.*, an NOVX protein or anti-NOVX antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

The nucleic acid molecules of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (*see, e.g.,* U.S. Patent No. 5,328,470) or by stereotactic injection (*see, e.g.*, Chen, *et al.*, 1994. *Proc. Natl. Acad. Sci. USA* 91: 3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.*, retroviral vectors, the pharmaceutical preparation can include one or more cells that produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

Screening and Detection Methods

The isolated nucleic acid molecules of the invention can be used to express NOVX protein (*e.g.*, via a recombinant expression vector in a host cell in gene therapy applications), to detect NOVX mRNA (*e.g.*, in a biological sample) or a genetic lesion in an NOVX gene, and to modulate NOVX activity, as described further, below. In addition, the NOVX proteins can be used to screen drugs or compounds that modulate the NOVX protein activity or expression as well as to treat disorders characterized by insufficient or excessive production of NOVX protein or production of NOVX protein forms that have decreased or aberrant activity compared to NOVX wild-type protein (*e.g.*; diabetes (regulates insulin release); obesity (binds and transport lipids); metabolic disturbances associated with obesity, the metabolic syndrome X as well as anorexia and wasting disorders associated with chronic diseases and various cancers, and infectious disease(possesses anti-microbial activity) and the various dyslipidemias. In addition, the anti-NOVX antibodies of the invention can be used to detect and isolate NOVX proteins and modulate NOVX activity. In yet a further aspect, the invention can be used in methods to influence appetite, absorption of nutrients and the disposition of metabolic substrates in both a positive and negative fashion.

The invention further pertains to novel agents identified by the screening assays described herein and uses thereof for treatments as described, *supra*.

Screening Assays

The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides,

peptidomimetics, small molecules or other drugs) that bind to NOVX proteins or have a stimulatory or inhibitory effect on, *e.g.*, NOVX protein expression or NOVX protein activity. The invention also includes compounds identified in the screening assays described herein.

In one embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of the membrane-bound form of an NOVX protein or polypeptide or biologically-active portion thereof. The test compounds of the invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the "one-bead one-compound" library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds. *See, e.g.,* Lam, 1997. *Anticancer Drug Design* 12: 145.

A "small molecule" as used herein, is meant to refer to a composition that has a molecular weight of less than about 5 kD and most preferably less than about 4 kD. Small molecules can be, *e.g.*, nucleic acids, peptides, polypeptides, peptidomimetics, carbohydrates, lipids or other organic or inorganic molecules. Libraries of chemical and/or biological mixtures, such as fungal, bacterial, or algal extracts, are known in the art and can be screened with any of the assays of the invention.

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt, *et al.*, 1993. *Proc. Natl. Acad. Sci. U.S.A.* 90: 6909; Erb, *et al.*, 1994. *Proc. Natl. Acad. Sci. U.S.A.* 91: 11422; Zuckermann, *et al.*, 1994. *J. Med. Chem.* 37: 2678; Cho, *et al.*, 1993. *Science* 261: 1303; Carrell, *et al.*, 1994. *Angew. Chem. Int. Ed. Engl.* 33: 2059; Carell, *et al.*, 1994. *Angew. Chem. Int. Ed. Engl.* 33: 2061; and Gallop, *et al.*, 1994. *J. Med. Chem.* 37: 1233.

Libraries of compounds may be presented in solution (*e.g.*, Houghten, 1992. *Biotechniques* 13: 412-421), or on beads (Lam, 1991. *Nature* 354: 82-84), on chips (Fodor, 1993. *Nature* 364: 555-556), bacteria (Ladner, U.S. Patent No. 5,223,409), spores (Ladner, U.S. Patent 5,233,409), plasmids (Cull, *et al.*, 1992. *Proc. Natl. Acad. Sci. USA* 89: 1865-1869) or on phage (Scott and Smith, 1990. *Science* 249: 386-390; Devlin, 1990. *Science* 249: 404-406; Cwirla, *et al.*, 1990. *Proc. Natl. Acad. Sci. U.S.A.* 87: 6378-6382; Felici, 1991. *J. Mol. Biol.* 222: 301-310; Ladner, U.S. Patent No. 5,233,409.).

In one embodiment, an assay is a cell-based assay in which a cell which expresses a membrane-bound form of NOVX protein, or a biologically-active portion thereof, on the cell

surface is contacted with a test compound and the ability of the test compound to bind to an NOVX protein determined. The cell, for example, can of mammalian origin or a yeast cell. Determining the ability of the test compound to bind to the NOVX protein can be accomplished, for example, by coupling the test compound with a radioisotope or enzymatic label such that binding of the test compound to the NOVX protein or biologically-active portion thereof can be determined by detecting the labeled compound in a complex. For example, test compounds can be labeled with ^{125}I, ^{35}S, ^{14}C, or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, test compounds can be enzymatically-labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product. In one embodiment, the assay comprises contacting a cell which expresses a membrane-bound form of NOVX protein, or a biologically-active portion thereof, on the cell surface with a known compound which binds NOVX to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with an NOVX protein, wherein determining the ability of the test compound to interact with an NOVX protein comprises determining the ability of the test compound to preferentially bind to NOVX protein or a biologically-active portion thereof as compared to the known compound.

In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a membrane-bound form of NOVX protein, or a biologically-active portion thereof, on the cell surface with a test compound and determining the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the NOVX protein or biologically-active portion thereof. Determining the ability of the test compound to modulate the activity of NOVX or a biologically-active portion thereof can be accomplished, for example, by determining the ability of the NOVX protein to bind to or interact with an NOVX target molecule. As used herein, a "target molecule" is a molecule with which an NOVX protein binds or interacts in nature, for example, a molecule on the surface of a cell which expresses an NOVX interacting protein, a molecule on the surface of a second cell, a molecule in the extracellular milieu, a molecule associated with the internal surface of a cell membrane or a cytoplasmic molecule. An NOVX target molecule can be a non-NOVX molecule or an NOVX protein or polypeptide of the invention. In one embodiment, an NOVX target molecule is a component of a signal transduction pathway that facilitates transduction of an extracellular signal (*e.g.* a signal generated by binding of a compound to a membrane-bound NOVX molecule) through the cell membrane and into the cell. The target, for example, can be

a second intercellular protein that has catalytic activity or a protein that facilitates the association of downstream signaling molecules with NOVX.

Determining the ability of the NOVX protein to bind to or interact with an NOVX target molecule can be accomplished by one of the methods described above for determining direct binding. In one embodiment, determining the ability of the NOVX protein to bind to or interact with an NOVX target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (*i.e.* intracellular Ca^{2+}, diacylglycerol, IP_3, etc.), detecting catalytic/enzymatic activity of the target an appropriate substrate, detecting the induction of a reporter gene (comprising an NOVX-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, *e.g.*, luciferase), or detecting a cellular response, for example, cell survival, cellular differentiation, or cell proliferation.

In yet another embodiment, an assay of the invention is a cell-free assay comprising contacting an NOVX protein or biologically-active portion thereof with a test compound and determining the ability of the test compound to bind to the NOVX protein or biologically-active portion thereof. Binding of the test compound to the NOVX protein can be determined either directly or indirectly as described above. In one such embodiment, the assay comprises contacting the NOVX protein or biologically-active portion thereof with a known compound which binds NOVX to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with an NOVX protein, wherein determining the ability of the test compound to interact with an NOVX protein comprises determining the ability of the test compound to preferentially bind to NOVX or biologically-active portion thereof as compared to the known compound.

In still another embodiment, an assay is a cell-free assay comprising contacting NOVX protein or biologically-active portion thereof with a test compound and determining the ability of the test compound to modulate (*e.g.* stimulate or inhibit) the activity of the NOVX protein or biologically-active portion thereof. Determining the ability of the test compound to modulate the activity of NOVX can be accomplished, for example, by determining the ability of the NOVX protein to bind to an NOVX target molecule by one of the methods described above for determining direct binding. In an alternative embodiment, determining the ability of the test compound to modulate the activity of NOVX protein can be accomplished by determining the ability of the NOVX protein further modulate an NOVX target molecule. For

example, the catalytic/enzymatic activity of the target molecule on an appropriate substrate can be determined as described, *supra*.

In yet another embodiment, the cell-free assay comprises contacting the NOVX protein or biologically-active portion thereof with a known compound which binds NOVX protein to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with an NOVX protein, wherein determining the ability of the test compound to interact with an NOVX protein comprises determining the ability of the NOVX protein to preferentially bind to or modulate the activity of an NOVX target molecule.

The cell-free assays of the invention are amenable to use of both the soluble form or the membrane-bound form of NOVX protein. In the case of cell-free assays comprising the membrane-bound form of NOVX protein, it may be desirable to utilize a solubilizing agent such that the membrane-bound form of NOVX protein is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton® X-100, Triton® X-114, Thesit®, Isotridecypoly(ethylene glycol ether)$_n$, N-dodecyl--N,N-dimethyl-3-ammonio-1-propane sulfonate, 3-(3-cholamidopropyl) dimethylamminiol-1-propane sulfonate (CHAPS), or 3-(3-cholamidopropyl)dimethylamminiol-2-hydroxy-1-propane sulfonate (CHAPSO).

In more than one embodiment of the above assay methods of the invention, it may be desirable to immobilize either NOVX protein or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to NOVX protein, or interaction of NOVX protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtiter plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided that adds a domain that allows one or both of the proteins to be bound to a matrix. For example, GST-NOVX fusion proteins or GST-target fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, that are then combined with the test compound or the test compound and either the non-adsorbed target protein or NOVX protein, and the mixture is incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtiter plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex

determined either directly or indirectly, for example, as described, *supra*. Alternatively, the complexes can be dissociated from the matrix, and the level of NOVX protein binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either the NOVX protein or its target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated NOVX protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques well-known within the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, Ill.), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with NOVX protein or target molecules, but which do not interfere with binding of the NOVX protein to its target molecule, can be derivatized to the wells of the plate, and unbound target or NOVX protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the NOVX protein or target molecule, as well as enzyme-linked assays that rely on detecting an enzymatic activity associated with the NOVX protein or target molecule.

In another embodiment, modulators of NOVX protein expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of NOVX mRNA or protein in the cell is determined. The level of expression of NOVX mRNA or protein in the presence of the candidate compound is compared to the level of expression of NOVX mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of NOVX mRNA or protein expression based upon this comparison. For example, when expression of NOVX mRNA or protein is greater (*i.e.*, statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of NOVX mRNA or protein expression. Alternatively, when expression of NOVX mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of NOVX mRNA or protein expression. The level of NOVX mRNA or protein expression in the cells can be determined by methods described herein for detecting NOVX mRNA or protein.

In yet another aspect of the invention, the NOVX proteins can be used as "bait proteins" in a two-hybrid assay or three hybrid assay (*see, e.g.*, U.S. Patent No. 5,283,317; Zervos, *et al.*, 1993. *Cell* 72: 223-232; Madura, *et al.*, 1993. *J. Biol. Chem.* 268: 12046-12054;

Bartel, *et al.*, 1993. *Biotechniques* 14: 920-924; Iwabuchi, *et al.*, 1993. *Oncogene* 8: 1693-1696; and Brent WO 94/10300), to identify other proteins that bind to or interact with NOVX ("NOVX-binding proteins" or "NOVX-bp") and modulate NOVX activity. Such NOVX-binding proteins are also likely to be involved in the propagation of signals by the NOVX proteins as, for example, upstream or downstream elements of the NOVX pathway.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for NOVX is fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming an NOVX-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) that is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene that encodes the protein which interacts with NOVX.

The invention further pertains to novel agents identified by the aforementioned screening assays and uses thereof for treatments as described herein.

Detection Assays

Portions or fragments of the cDNA sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. By way of example, and not of limitation, these sequences can be used to: (*i*) map their respective genes on a chromosome; and, thus, locate gene regions associated with genetic disease; (*ii*) identify an individual from a minute biological sample (tissue typing); and (*iii*) aid in forensic identification of a biological sample. Some of these applications are described in the subsections, below.

Chromosome Mapping

Once the sequence (or a portion of the sequence) of a gene has been isolated, this sequence can be used to map the location of the gene on a chromosome. This process is called chromosome mapping. Accordingly, portions or fragments of the NOVX sequences, SEQ ID

NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, or fragments or derivatives thereof, can be used to map the location of the NOVX genes, respectively, on a chromosome. The mapping of the NOVX sequences to chromosomes is an important first step in correlating these sequences with genes associated with disease.

Briefly, NOVX genes can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp in length) from the NOVX sequences. Computer analysis of the NOVX, sequences can be used to rapidly select primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers can then be used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the NOVX sequences will yield an amplified fragment.

Somatic cell hybrids are prepared by fusing somatic cells from different mammals (*e.g.*, human and mouse cells). As hybrids of human and mouse cells grow and divide, they gradually lose human chromosomes in random order, but retain the mouse chromosomes. By using media in which mouse cells cannot grow, because they lack a particular enzyme, but in which human cells can, the one human chromosome that contains the gene encoding the needed enzyme will be retained. By using various media, panels of hybrid cell lines can be established. Each cell line in a panel contains either a single human chromosome or a small number of human chromosomes, and a full set of mouse chromosomes, allowing easy mapping of individual genes to specific human chromosomes. *See, e.g.,* D'Eustachio, *et al.*, 1983. *Science* 220: 919-924. Somatic cell hybrids containing only fragments of human chromosomes can also be produced by using human chromosomes with translocations and deletions.

PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular sequence to a particular chromosome. Three or more sequences can be assigned per day using a single thermal cycler. Using the NOVX sequences to design oligonucleotide primers, sub-localization can be achieved with panels of fragments from specific chromosomes.

Fluorescence *in situ* hybridization (FISH) of a DNA sequence to a metaphase chromosomal spread can further be used to provide a precise chromosomal location in one step. Chromosome spreads can be made using cells whose division has been blocked in metaphase by a chemical like colcemid that disrupts the mitotic spindle. The chromosomes can be treated briefly with trypsin, and then stained with Giemsa. A pattern of light and dark bands develops on each chromosome, so that the chromosomes can be identified individually. The FISH technique can be used with a DNA sequence as short as 500 or 600 bases.

However, clones larger than 1,000 bases have a higher likelihood of binding to a unique chromosomal location with sufficient signal intensity for simple detection. Preferably 1,000 bases, and more preferably 2,000 bases, will suffice to get good results at a reasonable amount of time. For a review of this technique, *see,* Verma, *et al.*, HUMAN CHROMOSOMES: A MANUAL OF BASIC TECHNIQUES (Pergamon Press, New York 1988).

Reagents for chromosome mapping can be used individually to mark a single chromosome or a single site on that chromosome, or panels of reagents can be used for marking multiple sites and/or multiple chromosomes. Reagents corresponding to noncoding regions of the genes actually are preferred for mapping purposes. Coding sequences are more likely to be conserved within gene families, thus increasing the chance of cross hybridizations during chromosomal mapping.

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found, *e.g.,* in McKusick, MENDELIAN INHERITANCE IN MAN, available on-line through Johns Hopkins University Welch Medical Library). The relationship between genes and disease, mapped to the same chromosomal region, can then be identified through linkage analysis (co-inheritance of physically adjacent genes), described in, *e.g.,* Egeland, *et al.*, 1987. *Nature*, 325: 783-787.

Moreover, differences in the DNA sequences between individuals affected and unaffected with a disease associated with the NOVX gene, can be determined. If a mutation is observed in some or all of the affected individuals but not in any unaffected individuals, then the mutation is likely to be the causative agent of the particular disease. Comparison of affected and unaffected individuals generally involves first looking for structural alterations in the chromosomes, such as deletions or translocations that are visible from chromosome spreads or detectable using PCR based on that DNA sequence. Ultimately, complete sequencing of genes from several individuals can be performed to confirm the presence of a mutation and to distinguish mutations from polymorphisms.

Tissue Typing

The NOVX sequences of the invention can also be used to identify individuals from minute biological samples. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identification. The sequences of the invention are useful as additional DNA markers for RFLP ("restriction fragment length polymorphisms," described in U.S. Patent No. 5,272,057).

Furthermore, the sequences of the invention can be used to provide an alternative technique that determines the actual base-by-base DNA sequence of selected portions of an individual's genome. Thus, the NOVX sequences described herein can be used to prepare two PCR primers from the 5'- and 3'-termini of the sequences. These primers can then be used to amplify an individual's DNA and subsequently sequence it.

Panels of corresponding DNA sequences from individuals, prepared in this manner, can provide unique individual identifications, as each individual will have a unique set of such DNA sequences due to allelic differences. The sequences of the invention can be used to obtain such identification sequences from individuals and from tissue. The NOVX sequences of the invention uniquely represent portions of the human genome. Allelic variation occurs to some degree in the coding regions of these sequences, and to a greater degree in the noncoding regions. It is estimated that allelic variation between individual humans occurs with a frequency of about once per each 500 bases. Much of the allelic variation is due to single nucleotide polymorphisms (SNPs), which include restriction fragment length polymorphisms (RFLPs).

Each of the sequences described herein can, to some degree, be used as a standard against which DNA from an individual can be compared for identification purposes. Because greater numbers of polymorphisms occur in the noncoding regions, fewer sequences are necessary to differentiate individuals. The noncoding sequences can comfortably provide positive individual identification with a panel of perhaps 10 to 1,000 primers that each yield a noncoding amplified sequence of 100 bases. If predicted coding sequences, such as those in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43 are used, a more appropriate number of primers for positive individual identification would be 500-2,000.

Predictive Medicine

The invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the invention relates to diagnostic assays for determining NOVX protein and/or nucleic acid expression as well as NOVX activity, in the context of a biological sample (*e.g.*, blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a disease or disorder, or is at risk of developing a disorder, associated with aberrant NOVX expression or activity. The disorders include metabolic disorders, diabetes, obesity, infectious

disease, anorexia, cancer-associated cachexia, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders, and the various dyslipidemias, metabolic disturbances associated with obesity, the metabolic syndrome X and wasting disorders associated with chronic diseases and various cancers. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder associated with NOVX protein, nucleic acid expression or activity. For example, mutations in an NOVX gene can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a disorder characterized by or associated with NOVX protein, nucleic acid expression, or biological activity.

Another aspect of the invention provides methods for determining NOVX protein, nucleic acid expression or activity in an individual to thereby select appropriate therapeutic or prophylactic agents for that individual (referred to herein as "pharmacogenomics"). Pharmacogenomics allows for the selection of agents (*e.g.*, drugs) for therapeutic or prophylactic treatment of an individual based on the genotype of the individual (*e.g.*, the genotype of the individual examined to determine the ability of the individual to respond to a particular agent.)

Yet another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs, compounds) on the expression or activity of NOVX in clinical trials.

These and other agents are described in further detail in the following sections.

Diagnostic Assays

An exemplary method for detecting the presence or absence of NOVX in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of detecting NOVX protein or nucleic acid (*e.g.*, mRNA, genomic DNA) that encodes NOVX protein such that the presence of NOVX is detected in the biological sample. An agent for detecting NOVX mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to NOVX mRNA or genomic DNA. The nucleic acid probe can be, for example, a full-length NOVX nucleic acid, such as the nucleic acid of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41 and 43, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to NOVX mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

An agent for detecting NOVX protein is an antibody capable of binding to NOVX protein, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or $F(ab')_2$) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently-labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently-labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. That is, the detection method of the invention can be used to detect NOVX mRNA, protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of NOVX mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of NOVX protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, and immunofluorescence. *In vitro* techniques for detection of NOVX genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of NOVX protein include introducing into a subject a labeled anti-NOVX antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

In one embodiment, the biological sample contains protein molecules from the test subject. Alternatively, the biological sample can contain mRNA molecules from the test subject or genomic DNA molecules from the test subject. A preferred biological sample is a peripheral blood leukocyte sample isolated by conventional means from a subject.

In another embodiment, the methods further involve obtaining a control biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting NOVX protein, mRNA, or genomic DNA, such that the presence of NOVX protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of NOVX protein, mRNA or genomic DNA in the control sample with the presence of NOVX protein, mRNA or genomic DNA in the test sample.

The invention also encompasses kits for detecting the presence of NOVX in a biological sample. For example, the kit can comprise: a labeled compound or agent capable of detecting NOVX protein or mRNA in a biological sample; means for determining the amount

of NOVX in the sample; and means for comparing the amount of NOVX in the sample with a standard. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect NOVX protein or nucleic acid.

Prognostic Assays

The diagnostic methods described herein can furthermore be utilized to identify subjects having or at risk of developing a disease or disorder associated with aberrant NOVX expression or activity. For example, the assays described herein, such as the preceding diagnostic assays or the following assays, can be utilized to identify a subject having or at risk of developing a disorder associated with NOVX protein, nucleic acid expression or activity. Alternatively, the prognostic assays can be utilized to identify a subject having or at risk for developing a disease or disorder. Thus, the invention provides a method for identifying a disease or disorder associated with aberrant NOVX expression or activity in which a test sample is obtained from a subject and NOVX protein or nucleic acid (*e.g.*, mRNA, genomic DNA) is detected, wherein the presence of NOVX protein or nucleic acid is diagnostic for a subject having or at risk of developing a disease or disorder associated with aberrant NOVX expression or activity. As used herein, a "test sample" refers to a biological sample obtained from a subject of interest. For example, a test sample can be a biological fluid (*e.g.*, serum), cell sample, or tissue.

Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) to treat a disease or disorder associated with aberrant NOVX expression or activity. For example, such methods can be used to determine whether a subject can be effectively treated with an agent for a disorder. Thus, the invention provides methods for determining whether a subject can be effectively treated with an agent for a disorder associated with aberrant NOVX expression or activity in which a test sample is obtained and NOVX protein or nucleic acid is detected (*e.g.*, wherein the presence of NOVX protein or nucleic acid is diagnostic for a subject that can be administered the agent to treat a disorder associated with aberrant NOVX expression or activity).

The methods of the invention can also be used to detect genetic lesions in an NOVX gene, thereby determining if a subject with the lesioned gene is at risk for a disorder characterized by aberrant cell proliferation and/or differentiation. In various embodiments, the methods include detecting, in a sample of cells from the subject, the presence or absence of a

genetic lesion characterized by at least one of an alteration affecting the integrity of a gene encoding an NOVX-protein, or the misexpression of the NOVX gene. For example, such genetic lesions can be detected by ascertaining the existence of at least one of: (*i*) a deletion of one or more nucleotides from an NOVX gene; (*ii*) an addition of one or more nucleotides to an NOVX gene; (*iii*) a substitution of one or more nucleotides of an NOVX gene, (*iv*) a chromosomal rearrangement of an NOVX gene; (*v*) an alteration in the level of a messenger RNA transcript of an NOVX gene, (*vi*) aberrant modification of an NOVX gene, such as of the methylation pattern of the genomic DNA, (*vii*) the presence of a non-wild-type splicing pattern of a messenger RNA transcript of an NOVX gene, (*viii*) a non-wild-type level of an NOVX protein, (*ix*) allelic loss of an NOVX gene, and (*x*) inappropriate post-translational modification of an NOVX protein. As described herein, there are a large number of assay techniques known in the art which can be used for detecting lesions in an NOVX gene. A preferred biological sample is a peripheral blood leukocyte sample isolated by conventional means from a subject. However, any biological sample containing nucleated cells may be used, including, for example, buccal mucosal cells.

In certain embodiments, detection of the lesion involves the use of a probe/primer in a polymerase chain reaction (PCR) (*see, e.g.*, U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (*see, e.g.*, Landegran, *et al.*, 1988. *Science* 241: 1077-1080; and Nakazawa, *et al.*, 1994. *Proc. Natl. Acad. Sci. USA* 91: 360-364), the latter of which can be particularly useful for detecting point mutations in the NOVX-gene (*see,* Abravaya, *et al.*, 1995. *Nucl. Acids Res.* 23: 675-682). This method can include the steps of collecting a sample of cells from a patient, isolating nucleic acid (*e.g.*, genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers that specifically hybridize to an NOVX gene under conditions such that hybridization and amplification of the NOVX gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

Alternative amplification methods include: self sustained sequence replication (*see,* Guatelli, *et al.*, 1990. *Proc. Natl. Acad. Sci. USA* 87: 1874-1878), transcriptional amplification system (*see,* Kwoh, *et al.*, 1989. *Proc. Natl. Acad. Sci. USA* 86: 1173-1177); Qβ Replicase (*see,* Lizardi, *et al*, 1988. *BioTechnology* 6: 1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to

those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In an alternative embodiment, mutations in an NOVX gene from a sample cell can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes (*see, e.g.,* U.S. Patent No. 5,493,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

In other embodiments, genetic mutations in NOVX can be identified by hybridizing a sample and control nucleic acids, *e.g.*, DNA or RNA, to high-density arrays containing hundreds or thousands of oligonucleotides probes. *See, e.g.,* Cronin, *et al.*, 1996. *Human Mutation* 7: 244-255; Kozal, *et al.*, 1996. *Nat. Med.* 2: 753-759. For example, genetic mutations in NOVX can be identified in two dimensional arrays containing light-generated DNA probes as described in Cronin, *et al.*, *supra*. Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential overlapping probes. This step allows the identification of point mutations. This is followed by a second hybridization array that allows the characterization of specific mutations by using smaller, specialized probe arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the NOVX gene and detect mutations by comparing the sequence of the sample NOVX with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxim and Gilbert, 1977. *Proc. Natl. Acad. Sci. USA* 74: 560 or Sanger, 1977. *Proc. Natl. Acad. Sci. USA* 74: 5463. It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the diagnostic assays (*see, e.g.,* Naeve, *et al.*, 1995. *Biotechniques* 19: 448), including sequencing by mass spectrometry (see, *e.g.*, PCT International Publication No. WO 94/16101; Cohen, *et al.*, 1996. *Adv. Chromatography* 36: 127-162; and Griffin, *et al.*, 1993. *Appl. Biochem. Biotechnol.* 38: 147-159).

Other methods for detecting mutations in the NOVX gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes. *See, e.g.,* Myers, *et al.*, 1985. *Science* 230: 1242. In general, the art technique of "mismatch cleavage" starts by providing heteroduplexes of formed by hybridizing (labeled) RNA or DNA containing the wild-type NOVX sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent that cleaves single-stranded regions of the duplex such as which will exist due to basepair mismatches between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S_1 nuclease to enzymatically digesting the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. *See, e.g.,* Cotton, *et al.*, 1988. *Proc. Natl. Acad. Sci. USA* 85: 4397; Saleeba, *et al.*, 1992. *Methods Enzymol.* 217: 286-295. In an embodiment, the control DNA or RNA can be labeled for detection.

In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in NOVX cDNAs obtained from samples of cells. For example, the mutY enzyme of *E. coli* cleaves A at G/A mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches. *See, e.g.,* Hsu, *et al.*, 1994. *Carcinogenesis* 15: 1657-1662. According to an exemplary embodiment, a probe based on an NOVX sequence, *e.g.*, a wild-type NOVX sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the like. *See, e.g.,* U.S. Patent No. 5,459,039.

In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in NOVX genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids. *See, e.g.,* Orita, *et al.*, 1989. *Proc Natl. Acad. Sci. USA*: 86: 2766; Cotton, 1993. *Mutat. Res.* 285: 125-144; Hayashi, 1992. *Genet. Anal. Tech. Appl.* 9: 73-79. Single-stranded DNA fragments of sample and control NOVX nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection

of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In one embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility. *See, e.g.,* Keen, *et al.*, 1991. *Trends Genet.* 7: 5.

In yet another embodiment, the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE). *See, e.g.,* Myers, *et al.,* 1985. *Nature* 313: 495. When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA. *See, e.g.,* Rosenbaum and Reissner, 1987. *Biophys. Chem.* 265: 12753.

Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions that permit hybridization only if a perfect match is found. *See, e.g.,* Saiki, *et al.*, 1986. *Nature* 324: 163; Saiki, *et al.*, 1989. *Proc. Natl. Acad. Sci. USA* 86: 6230. Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA.

Alternatively, allele specific amplification technology that depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization; *see, e.g.,* Gibbs, *et al.*, 1989. *Nucl. Acids Res.* 17: 2437-2448) or at the extreme 3'-terminus of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (*see, e.g.,* Prossner, 1993. *Tibtech.* 11: 238). In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection. *See, e.g.,* Gasparini, *et al.,* 1992. *Mol. Cell Probes* 6: 1. It is anticipated that in certain embodiments amplification may also be performed using *Taq* ligase for amplification. *See, e.g.,* Barany, 1991. *Proc. Natl. Acad. Sci. USA* 88: 189. In such cases, ligation will occur only if there is a

perfect match at the 3'-terminus of the 5' sequence, making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits comprising at least one probe nucleic acid or antibody reagent described herein, which may be conveniently used, *e.g.*, in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness involving an NOVX gene.

Furthermore, any cell type or tissue, preferably peripheral blood leukocytes, in which NOVX is expressed may be utilized in the prognostic assays described herein. However, any biological sample containing nucleated cells may be used, including, for example, buccal mucosal cells.

Pharmacogenomics

Agents, or modulators that have a stimulatory or inhibitory effect on NOVX activity (*e.g.*, NOVX gene expression), as identified by a screening assay described herein can be administered to individuals to treat (prophylactically or therapeutically) disorders (The disorders include metabolic disorders, diabetes, obesity, infectious disease, anorexia, cancer-associated cachexia, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders, and the various dyslipidemias, metabolic disturbances associated with obesity, the metabolic syndrome X and wasting disorders associated with chronic diseases and various cancers.) In conjunction with such treatment, the pharmacogenomics (*i.e.*, the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) of the individual may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, the pharmacogenomics of the individual permits the selection of effective agents (*e.g.*, drugs) for prophylactic or therapeutic treatments based on a consideration of the individual's genotype. Such pharmacogenomics can further be used to determine appropriate dosages and therapeutic regimens. Accordingly, the activity of NOVX protein, expression of NOVX nucleic acid, or mutation content of NOVX genes in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual.

Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See

e.g., Eichelbaum, 1996. *Clin. Exp. Pharmacol. Physiol.*, 23: 983-985; Linder, 1997. *Clin. Chem.*, 43: 254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common inherited enzymopathy in which the main clinical complication is hemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. At the other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the activity of NOVX protein, expression of NOVX nucleic acid, or mutation content of NOVX genes in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with an NOVX modulator, such as a modulator identified by one of the exemplary screening assays described herein.

Monitoring of Effects During Clinical Trials

Monitoring the influence of agents (*e.g.*, drugs, compounds) on the expression or activity of NOVX (*e.g.*, the ability to modulate aberrant cell proliferation and/or differentiation) can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent determined by a screening assay as described herein to increase NOVX gene expression, protein levels, or upregulate NOVX activity, can be monitored in clinical trails of subjects exhibiting decreased NOVX gene expression, protein levels, or downregulated NOVX activity. Alternatively, the effectiveness of an agent determined by a screening assay to decrease NOVX gene expression, protein levels, or downregulate NOVX activity, can be monitored in clinical trails of subjects exhibiting increased NOVX gene expression, protein levels, or upregulated NOVX activity. In such clinical trials, the expression or activity of NOVX and, preferably, other genes that have been implicated in, for example, a cellular proliferation or immune disorder can be used as a "read out" or markers of the immune responsiveness of a particular cell.

By way of example, and not of limitation, genes, including NOVX, that are modulated in cells by treatment with an agent (*e.g.*, compound, drug or small molecule) that modulates NOVX activity (*e.g.*, identified in a screening assay as described herein) can be identified. Thus, to study the effect of agents on cellular proliferation disorders, for example, in a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of NOVX and other genes implicated in the disorder. The levels of gene expression (*i.e.*, a gene expression pattern) can be quantified by Northern blot analysis or RT-PCR, as described herein, or alternatively by measuring the amount of protein produced, by one of the methods as described herein, or by measuring the levels of activity of NOVX or other genes. In this manner, the gene expression pattern can serve as a marker, indicative of the physiological response of the cells to the agent. Accordingly, this response state may be determined before, and at various points during, treatment of the individual with the agent.

In one embodiment, the invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, protein, peptide, peptidomimetic, nucleic acid, small molecule, or other drug candidate identified by the screening assays described herein) comprising the steps of (*i*) obtaining a pre-administration sample from a subject prior to administration of the agent; (*ii*) detecting the level of expression of an NOVX protein, mRNA, or genomic DNA in the preadministration sample; (*iii*) obtaining one or more post-administration samples from the subject; (*iv*) detecting the level of

expression or activity of the NOVX protein, mRNA, or genomic DNA in the post-administration samples; (*v*) comparing the level of expression or activity of the NOVX protein, mRNA, or genomic DNA in the pre-administration sample with the NOVX protein, mRNA, or genomic DNA in the post administration sample or samples; and (*vi*) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of NOVX to higher levels than detected, *i.e.*, to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of NOVX to lower levels than detected, *i.e.*, to decrease the effectiveness of the agent.

Methods of Treatment

The invention provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated with aberrant NOVX expression or activity. The disorders include cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, scleroderma, obesity, transplantation, adrenoleukodystrophy, congenital adrenal hyperplasia, prostate cancer, neoplasm; adenocarcinoma, lymphoma, uterus cancer, fertility, hemophilia, hypercoagulation, idiopathic thrombocytopenic purpura, immunodeficiencies, graft versus host disease, AIDS, bronchial asthma, Crohn's disease; multiple sclerosis, treatment of Albright Hereditary Ostoeodystrophy, and other diseases, disorders and conditions of the like.

These methods of treatment will be discussed more fully, below.

Disease and Disorders

Diseases and disorders that are characterized by increased (relative to a subject not suffering from the disease or disorder) levels or biological activity may be treated with Therapeutics that antagonize (*i.e.*, reduce or inhibit) activity. Therapeutics that antagonize activity may be administered in a therapeutic or prophylactic manner. Therapeutics that may be utilized include, but are not limited to: (*i*) an aforementioned peptide, or analogs, derivatives, fragments or homologs thereof; (*ii*) antibodies to an aforementioned peptide; (*iii*) nucleic acids encoding an aforementioned peptide; (*iv*) administration of antisense nucleic acid and nucleic acids that are "dysfunctional" (*i.e.*, due to a heterologous insertion within the coding sequences of coding sequences to an aforementioned peptide) that are utilized to

"knockout" endogenous function of an aforementioned peptide by homologous recombination (*see, e.g.,* Capecchi, 1989. *Science* 244: 1288-1292); or (*v*) modulators (*i.e.*, inhibitors, agonists and antagonists, including additional peptide mimetic of the invention or antibodies specific to a peptide of the invention) that alter the interaction between an aforementioned peptide and its binding partner.

Diseases and disorders that are characterized by decreased (relative to a subject not suffering from the disease or disorder) levels or biological activity may be treated with Therapeutics that increase (*i.e.*, are agonists to) activity. Therapeutics that upregulate activity may be administered in a therapeutic or prophylactic manner. Therapeutics that may be utilized include, but are not limited to, an aforementioned peptide, or analogs, derivatives, fragments or homologs thereof; or an agonist that increases bioavailability.

Increased or decreased levels can be readily detected by quantifying peptide and/or RNA, by obtaining a patient tissue sample (*e.g.,* from biopsy tissue) and assaying it *in vitro* for RNA or peptide levels, structure and/or activity of the expressed peptides (or mRNAs of an aforementioned peptide). Methods that are well-known within the art include, but are not limited to, immunoassays (*e.g.,* by Western blot analysis, immunoprecipitation followed by sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis, immunocytochemistry, etc.) and/or hybridization assays to detect expression of mRNAs (*e.g.,* Northern assays, dot blots, *in situ* hybridization, and the like).

Prophylactic Methods

In one aspect, the invention provides a method for preventing, in a subject, a disease or condition associated with an aberrant NOVX expression or activity, by administering to the subject an agent that modulates NOVX expression or at least one NOVX activity. Subjects at risk for a disease that is caused or contributed to by aberrant NOVX expression or activity can be identified by, for example, any or a combination of diagnostic or prognostic assays as described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of the NOVX aberrancy, such that a disease or disorder is prevented or, alternatively, delayed in its progression. Depending upon the type of NOVX aberrancy, for example, an NOVX agonist or NOVX antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein. The prophylactic methods of the invention are further discussed in the following subsections.

Therapeutic Methods

Another aspect of the invention pertains to methods of modulating NOVX expression or activity for therapeutic purposes. The modulatory method of the invention involves contacting a cell with an agent that modulates one or more of the activities of NOVX protein activity associated with the cell. An agent that modulates NOVX protein activity can be an agent as described herein, such as a nucleic acid or a protein, a naturally-occurring cognate ligand of an NOVX protein, a peptide, an NOVX peptidomimetic, or other small molecule. In one embodiment, the agent stimulates one or more NOVX protein activity. Examples of such stimulatory agents include active NOVX protein and a nucleic acid molecule encoding NOVX that has been introduced into the cell. In another embodiment, the agent inhibits one or more NOVX protein activity. Examples of such inhibitory agents include antisense NOVX nucleic acid molecules and anti-NOVX antibodies. These modulatory methods can be performed *in vitro* (*e.g.*, by culturing the cell with the agent) or, alternatively, *in vivo* (*e.g.*, by administering the agent to a subject). As such, the invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant expression or activity of an NOVX protein or nucleic acid molecule. In one embodiment, the method involves administering an agent (*e.g.*, an agent identified by a screening assay described herein), or combination of agents that modulates (*e.g.*, up-regulates or down-regulates) NOVX expression or activity. In another embodiment, the method involves administering an NOVX protein or nucleic acid molecule as therapy to compensate for reduced or aberrant NOVX expression or activity.

Stimulation of NOVX activity is desirable *in situ*ations in which NOVX is abnormally downregulated and/or in which increased NOVX activity is likely to have a beneficial effect. One example of such a situation is where a subject has a disorder characterized by aberrant cell proliferation and/or differentiation (*e.g.*, cancer or immune associated disorders). Another example of such a situation is where the subject has a gestational disease (*e.g.*, preclampsia).

Determination of the Biological Effect of the Therapeutic

In various embodiments of the invention, suitable *in vitro* or *in vivo* assays are performed to determine the effect of a specific Therapeutic and whether its administration is indicated for treatment of the affected tissue.

In various specific embodiments, *in vitro* assays may be performed with representative cells of the type(s) involved in the patient's disorder, to determine if a given Therapeutic exerts

the desired effect upon the cell type(s). Compounds for use in therapy may be tested in suitable animal model systems including, but not limited to rats, mice, chicken, cows, monkeys, rabbits, and the like, prior to testing in human subjects. Similarly, for *in vivo* testing, any of the animal model system known in the art may be used prior to administration to human subjects.

Prophylactic and Therapeutic Uses of the Compositions of the Invention

The NOVX nucleic acids and proteins of the invention are useful in potential prophylactic and therapeutic applications implicated in a variety of disorders including, but not limited to: metabolic disorders, diabetes, obesity, infectious disease, anorexia, cancer-associated cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, hematopoietic disorders, and the various dyslipidemias, metabolic disturbances associated with obesity, the metabolic syndrome X and wasting disorders associated with chronic diseases and various cancers.

As an example, a cDNA encoding the NOVX protein of the invention may be useful in gene therapy, and the protein may be useful when administered to a subject in need thereof. By way of non-limiting example, the compositions of the invention will have efficacy for treatment of patients suffering from: metabolic disorders, diabetes, obesity, infectious disease, anorexia, cancer-associated cachexia, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, hematopoietic disorders, and the various dyslipidemias.

Both the novel nucleic acid encoding the NOVX protein, and the NOVX protein of the invention, or fragments thereof, may also be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. A further use could be as an anti-bacterial molecule (*i.e.,* some peptides have been found to possess anti-bacterial properties). These materials are further useful in the generation of antibodies, which immunospecifically-bind to the novel substances of the invention for use in therapeutic or diagnostic methods.

The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

Examples

Example 1. Identification of NOVX clones

The novel NOVX target sequences identified in the present invention were subjected to the exon linking process to confirm the sequence. PCR primers were designed by starting at the most upstream sequence available, for the forward primer, and at the most downstream sequence available for the reverse primer. Table 16A shows the sequences of the PCR primers used for obtaining different clones. In each case, the sequence was examined, walking inward from the respective termini toward the coding sequence, until a suitable sequence that is either unique or highly selective was encountered, or, in the case of the reverse primer, until the stop codon was reached. Such primers were designed based on in silico predictions for the full length cDNA, part (one or more exons) of the DNA or protein sequence of the target sequence, or by translated homology of the predicted exons to closely related human sequences from other species. These primers were then employed in PCR amplification based on the following pool of human cDNAs: adrenal gland, bone marrow, brain - amygdala, brain - cerebellum, brain - hippocampus, brain - substantia nigra, brain - thalamus, brain -whole, fetal brain, fetal kidney, fetal liver, fetal lung, heart, kidney, lymphoma - Raji, mammary gland, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thyroid, trachea, uterus. Usually the resulting amplicons were gel purified, cloned and sequenced to high redundancy. The PCR product derived from exon linking was cloned into the pCR2.1 vector from Invitrogen. The resulting bacterial clone has an insert covering the entire open reading frame cloned into the pCR2.1 vector. Table 16B shows a list of these bacterial clones. The resulting sequences from all clones were assembled with themselves, with other fragments in CuraGen Corporation's database and with public ESTs. Fragments and ESTs were included as components for an assembly when the extent of their identity with another component of the assembly was at least 95% over 50 bp. In addition, sequence traces were evaluated manually and edited for corrections if appropriate. These procedures provide the sequence reported herein.

Table 12A. PCR Primers for Exon Linking

NOVX Clone	Primer 1 (5' - 3')	SEQ ID NO	Primer 2 (5' - 3')	SEQ ID NO
NOV6	CCATGTGGCAGCTGAGGCTTCAT	105	AAAGCCCCAGGTCCTCTTGCTAGCT	106
NOV7	GGATGAACCAGACTTTGAATAGCAGTG	107	GGCTCTCAAGCCCCCATCTC	108
NOV8	ATGCGAAGTCACTCTTACCTCTGATGAT	109	GGGAGCTGATCTTGAGTTATTTAACATAGC	110
NOV10a	CTGAATGGAACCATCACCAGC	111	ATCAGCACTATTTCTTCATGTGCAGG	112

Physical clone: Exons were predicted by homology and the intron/exon boundaries were determined using standard genetic rules. Exons were further selected and refined by

means of similarity determination using multiple BLAST (for example, tBlastN, BlastX, and BlastN) searches, and, in some instances, GeneScan and Grail. Expressed sequences from both public and proprietary databases were also added when available to further define and complete the gene sequence. The DNA sequence was then manually corrected for apparent inconsistencies thereby obtaining the sequences encoding the full-length protein.

Table 12B. Physical Clones for PCR products

NOVX Clone	Bacterial Clone
NOV7	Bacterial Clone: 120970::GMAP000808_A.698361.O8

Example 2. Quantitative expression analysis of clones in various cells and tissues

The quantitative expression of various clones was assessed using microtiter plates containing RNA samples from a variety of normal and pathology-derived cells, cell lines and tissues using real time quantitative PCR (RTQ PCR). RTQ PCR was performed on an Applied Biosystems ABI PRISM® 7700 or an ABI PRISM® 7900 HT Sequence Detection System. Various collections of samples are assembled on the plates, and referred to as Panel 1 (containing normal tissues and cancer cell lines), Panel 2 (containing samples derived from tissues from normal and cancer sources), Panel 3 (containing cancer cell lines), Panel 4 (containing cells and cell lines from normal tissues and cells related to inflammatory conditions), Panel 5D/5I (containing human tissues and cell lines with an emphasis on metabolic diseases), AI_comprehensive_panel (containing normal tissue and samples from autoinflammatory diseases), Panel CNSD.01 (containing samples from normal and diseased brains) and CNS_neurodegeneration_panel (containing samples from normal and Alzheimer's diseased brains).

RNA integrity from all samples is controlled for quality by visual assessment of agarose gel electropherograms using 28S and 18S ribosomal RNA staining intensity ratio as a guide (2:1 to 2.5:1 28s:18s) and the absence of low molecular weight RNAs that would be indicative of degradation products. Samples are controlled against genomic DNA contamination by RTQ PCR reactions run in the absence of reverse transcriptase using probe and primer sets designed to amplify across the span of a single exon.

First, the RNA samples were normalized to reference nucleic acids such as constitutively expressed genes (for example, β-actin and GAPDH). Normalized RNA (5 ul) was converted to cDNA and analyzed by RTQ-PCR using One Step RT-PCR Master Mix Reagents (Applied Biosystems; Catalog No. 4309169) and gene-specific primers according to the manufacturer's instructions.

In other cases, non-normalized RNA samples were converted to single strand cDNA (sscDNA) using Superscript II (Invitrogen Corporation; Catalog No. 18064-147) and random hexamers according to the manufacturer's instructions. Reactions containing up to 10 µg of total RNA were performed in a volume of 20 µl and incubated for 60 minutes at 42°C. This reaction can be scaled up to 50 µg of total RNA in a final volume of 100 µl. sscDNA samples are then normalized to reference nucleic acids as described previously, using 1X TaqMan® Universal Master mix (Applied Biosystems; catalog No. 4324020), following the manufacturer's instructions.

Probes and primers were designed for each assay according to Applied Biosystems Primer Express Software package (version I for Apple Computer's Macintosh Power PC) or a similar algorithm using the target sequence as input. Default settings were used for reaction conditions and the following parameters were set before selecting primers: primer concentration = 250 nM, primer melting temperature (Tm) range = 58°-60°C, primer optimal Tm = 59°C, maximum primer difference = 2°C, probe does not have 5'G, probe Tm must be 10°C greater than primer Tm, amplicon size 75bp to 100bp. The probes and primers selected (see below) were synthesized by Synthegen (Houston, TX, USA). Probes were double purified by HPLC to remove uncoupled dye and evaluated by mass spectroscopy to verify coupling of reporter and quencher dyes to the 5' and 3' ends of the probe, respectively. Their final concentrations were: forward and reverse primers, 900nM each, and probe, 200nM.

PCR conditions: When working with RNA samples, normalized RNA from each tissue and each cell line was spotted in each well of either a 96 well or a 384-well PCR plate (Applied Biosystems). PCR cocktails included either a single gene specific probe and primers set, or two multiplexed probe and primers sets (a set specific for the target clone and another gene-specific set multiplexed with the target probe). PCR reactions were set up using TaqMan® One-Step RT-PCR Master Mix (Applied Biosystems, Catalog No. 4313803) following manufacturer's instructions. Reverse transcription was performed at 48°C for 30 minutes followed by amplification/PCR cycles as follows: 95°C 10 min, then 40 cycles of 95°C for 15 seconds, 60°C for 1 minute. Results were recorded as CT values (cycle at which a given sample crosses a threshold level of fluorescence) using a log scale, with the difference in RNA concentration between a given sample and the sample with the lowest CT value being represented as 2 to the power of delta CT. The percent relative expression is then obtained by taking the reciprocal of this RNA difference and multiplying by 100.

When working with sscDNA samples, normalized sscDNA was used as described previously for RNA samples. PCR reactions containing one or two sets of probe and primers

were set up as described previously, using 1X TaqMan® Universal Master mix (Applied Biosystems; catalog No. 4324020), following the manufacturer's instructions. PCR amplification was performed as follows: 95°C 10 min, then 40 cycles of 95°C for 15 seconds, 60°C for 1 minute. Results were analyzed and processed as described previously.

Panels 1, 1.1, 1.2, and 1.3D

The plates for Panels 1, 1.1, 1.2 and 1.3D include 2 control wells (genomic DNA control and chemistry control) and 94 wells containing cDNA from various samples. The samples in these panels are broken into 2 classes: samples derived from cultured cell lines and samples derived from primary normal tissues. The cell lines are derived from cancers of the following types: lung cancer, breast cancer, melanoma, colon cancer, prostate cancer, CNS cancer, squamous cell carcinoma, ovarian cancer, liver cancer, renal cancer, gastric cancer and pancreatic cancer. Cell lines used in these panels are widely available through the American Type Culture Collection (ATCC), a repository for cultured cell lines, and were cultured using the conditions recommended by the ATCC. The normal tissues found on these panels are comprised of samples derived from all major organ systems from single adult individuals or fetuses. These samples are derived from the following organs: adult skeletal muscle, fetal skeletal muscle, adult heart, fetal heart, adult kidney, fetal kidney, adult liver, fetal liver, adult lung, fetal lung, various regions of the brain, the spleen, bone marrow, lymph node, pancreas, salivary gland, pituitary gland, adrenal gland, spinal cord, thymus, stomach, small intestine, colon, bladder, trachea, breast, ovary, uterus, placenta, prostate, testis and adipose.

In the results for Panels 1, 1.1, 1.2 and 1.3D, the following abbreviations are used:

ca. = carcinoma,
* = established from metastasis,
met = metastasis,
s cell var = small cell variant,
non-s = non-sm = non-small,
squam = squamous,
pl. eff = pl effusion = pleural effusion,
glio = glioma,
astro = astrocytoma, and
neuro = neuroblastoma.

General_screening_panel_v1.4

The plates for Panel 1.4 include 2 control wells (genomic DNA control and chemistry control) and 94 wells containing cDNA from various samples. The samples in Panel 1.4 are broken into 2 classes: samples derived from cultured cell lines and samples derived from primary normal tissues. The cell lines are derived from cancers of the following types: lung cancer, breast cancer, melanoma, colon cancer, prostate cancer, CNS cancer, squamous cell carcinoma, ovarian cancer, liver cancer, renal cancer, gastric cancer and pancreatic cancer. Cell lines used in Panel 1.4 are widely available through the American Type Culture Collection (ATCC), a repository for cultured cell lines, and were cultured using the conditions recommended by the ATCC. The normal tissues found on Panel 1.4 are comprised of pools of samples derived from all major organ systems from 2 to 5 different adult individuals or fetuses. These samples are derived from the following organs: adult skeletal muscle, fetal skeletal muscle, adult heart, fetal heart, adult kidney, fetal kidney, adult liver, fetal liver, adult lung, fetal lung, various regions of the brain, the spleen, bone marrow, lymph node, pancreas, salivary gland, pituitary gland, adrenal gland, spinal cord, thymus, stomach, small intestine, colon, bladder, trachea, breast, ovary, uterus, placenta, prostate, testis and adipose. Abbreviations are as described for Panels 1, 1.1, 1.2, and 1.3D.

Panels 2D and 2.2

The plates for Panels 2D and 2.2 generally include 2 control wells and 94 test samples composed of RNA or cDNA isolated from human tissue procured by surgeons working in close cooperation with the National Cancer Institute's Cooperative Human Tissue Network (CHTN) or the National Disease Research Initiative (NDRI). The tissues are derived from human malignancies and in cases where indicated many malignant tissues have "matched margins" obtained from noncancerous tissue just adjacent to the tumor. These are termed normal adjacent tissues and are denoted "NAT" in the results below. The tumor tissue and the "matched margins" are evaluated by two independent pathologists (the surgical pathologists and again by a pathologist at NDRI or CHTN). This analysis provides a gross histopathological assessment of tumor differentiation grade. Moreover, most samples include the original surgical pathology report that provides information regarding the clinical stage of the patient. These matched margins are taken from the tissue surrounding (i.e. immediately proximal) to the zone of surgery (designated "NAT", for normal adjacent tissue, in Table RR). In addition, RNA and cDNA samples were obtained from various human tissues derived from autopsies performed on elderly people or sudden death victims (accidents, etc.). These tissues were ascertained to be free of disease and were purchased from various commercial sources such as Clontech (Palo Alto, CA), Research Genetics, and Invitrogen.

Panel 3D

The plates of Panel 3D are comprised of 94 cDNA samples and two control samples. Specifically, 92 of these samples are derived from cultured human cancer cell lines, 2 samples of human primary cerebellar tissue and 2 controls. The human cell lines are generally obtained from ATCC (American Type Culture Collection), NCI or the German tumor cell bank and fall into the following tissue groups: Squamous cell carcinoma of the tongue, breast cancer, prostate cancer, melanoma, epidermoid carcinoma, sarcomas, bladder carcinomas, pancreatic cancers, kidney cancers, leukemias/lymphomas, ovarian/uterine/cervical, gastric, colon, lung and CNS cancer cell lines. In addition, there are two independent samples of cerebellum. These cells are all cultured under standard recommended conditions and RNA extracted using the standard procedures. The cell lines in panel 3D and 1.3D are of the most common cell lines used in the scientific literature.

Panels 4D, 4R, and 4.1D

Panel 4 includes samples on a 96 well plate (2 control wells, 94 test samples) composed of RNA (Panel 4R) or cDNA (Panels 4D/4.1D) isolated from various human cell lines or tissues related to inflammatory conditions. Total RNA from control normal tissues such as colon and lung (Stratagene, La Jolla, CA) and thymus and kidney (Clontech) was employed. Total RNA from liver tissue from cirrhosis patients and kidney from lupus patients was obtained from BioChain (Biochain Institute, Inc., Hayward, CA). Intestinal tissue for RNA preparation from patients diagnosed as having Crohn's disease and ulcerative colitis was obtained from the National Disease Research Interchange (NDRI) (Philadelphia, PA).

Astrocytes, lung fibroblasts, dermal fibroblasts, coronary artery smooth muscle cells, small airway epithelium, bronchial epithelium, microvascular dermal endothelial cells, microvascular lung endothelial cells, human pulmonary aortic endothelial cells, human umbilical vein endothelial cells were all purchased from Clonetics (Walkersville, MD) and grown in the media supplied for these cell types by Clonetics. These primary cell types were activated with various cytokines or combinations of cytokines for 6 and/or 12-14 hours, as indicated. The following cytokines were used; IL-1 beta at approximately 1-5ng/ml, TNF alpha at approximately 5-10ng/ml, IFN gamma at approximately 20-50ng/ml, IL-4 at approximately 5-10ng/ml, IL-9 at approximately 5-10ng/ml, IL-13 at approximately 5-10ng/ml. Endothelial cells were sometimes starved for various times by culture in the basal media from Clonetics with 0.1% serum.

Mononuclear cells were prepared from blood of employees at CuraGen Corporation, using Ficoll. LAK cells were prepared from these cells by culture in DMEM 5% FCS (Hyclone), 100μM non essential amino acids (Gibco/Life Technologies, Rockville, MD), 1mM sodium pyruvate (Gibco), mercaptoethanol $5.5x10^{-5}$M (Gibco), and 10mM Hepes (Gibco) and Interleukin 2 for 4-6 days. Cells were then either activated with 10-20ng/ml PMA and 1-2μg/ml ionomycin, IL-12 at 5-10ng/ml, IFN gamma at 20-50ng/ml and IL-18 at 5-10ng/ml for 6 hours. In some cases, mononuclear cells were cultured for 4-5 days in DMEM 5% FCS (Hyclone), 100μM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol $5.5x10^{-5}$M (Gibco), and 10mM Hepes (Gibco) with PHA (phytohemagglutinin) or PWM (pokeweed mitogen) at approximately 5μg/ml. Samples were taken at 24, 48 and 72 hours for RNA preparation. MLR (mixed lymphocyte reaction) samples were obtained by taking blood from two donors, isolating the mononuclear cells using Ficoll and mixing the isolated mononuclear cells 1:1 at a final concentration of approximately $2x10^{6}$cells/ml in DMEM 5% FCS (Hyclone), 100μM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol ($5.5x10^{-5}$M) (Gibco), and 10mM Hepes (Gibco). The MLR was cultured and samples taken at various time points ranging from 1- 7 days for RNA preparation.

Monocytes were isolated from mononuclear cells using CD14 Miltenyi Beads, +ve VS selection columns and a Vario Magnet according to the manufacturer's instructions. Monocytes were differentiated into dendritic cells by culture in DMEM 5% fetal calf serum (FCS) (Hyclone, Logan, UT), 100μM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol $5.5x10^{-5}$M (Gibco), and 10mM Hepes (Gibco), 50ng/ml GMCSF and 5ng/ml IL-4 for 5-7 days. Macrophages were prepared by culture of monocytes for 5-7 days in DMEM 5% FCS (Hyclone), 100μM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol $5.5x10^{-5}$M (Gibco), 10mM Hepes (Gibco) and 10% AB Human Serum or MCSF at approximately 50ng/ml. Monocytes, macrophages and dendritic cells were stimulated for 6 and 12-14 hours with lipopolysaccharide (LPS) at 100ng/ml. Dendritic cells were also stimulated with anti-CD40 monoclonal antibody (Pharmingen) at 10μg/ml for 6 and 12-14 hours.

CD4 lymphocytes, CD8 lymphocytes and NK cells were also isolated from mononuclear cells using CD4, CD8 and CD56 Miltenyi beads, positive VS selection columns and a Vario Magnet according to the manufacturer's instructions. CD45RA and CD45RO CD4 lymphocytes were isolated by depleting mononuclear cells of CD8, CD56, CD14 and CD19 cells using CD8, CD56, CD14 and CD19 Miltenyi beads and positive selection. CD45RO

beads were then used to isolate the CD45RO CD4 lymphocytes with the remaining cells being CD45RA CD4 lymphocytes. CD45RA CD4, CD45RO CD4 and CD8 lymphocytes were placed in DMEM 5% FCS (Hyclone), 100μM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol $5.5x10^{-5}$M (Gibco), and 10mM Hepes (Gibco) and plated at 10^6cells/ml onto Falcon 6 well tissue culture plates that had been coated overnight with 0.5μg/ml anti-CD28 (Pharmingen) and 3ug/ml anti-CD3 (OKT3, ATCC) in PBS. After 6 and 24 hours, the cells were harvested for RNA preparation. To prepare chronically activated CD8 lymphocytes, we activated the isolated CD8 lymphocytes for 4 days on anti-CD28 and anti-CD3 coated plates and then harvested the cells and expanded them in DMEM 5% FCS (Hyclone), 100μM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol $5.5x10^{-5}$M (Gibco), and 10mM Hepes (Gibco) and IL-2. The expanded CD8 cells were then activated again with plate bound anti-CD3 and anti-CD28 for 4 days and expanded as before. RNA was isolated 6 and 24 hours after the second activation and after 4 days of the second expansion culture. The isolated NK cells were cultured in DMEM 5% FCS (Hyclone), 100μM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol $5.5x10^{-5}$M (Gibco), and 10mM Hepes (Gibco) and IL-2 for 4-6 days before RNA was prepared.

To obtain B cells, tonsils were procured from NDRI. The tonsil was cut up with sterile dissecting scissors and then passed through a sieve. Tonsil cells were then spun down and resupended at 10^6cells/ml in DMEM 5% FCS (Hyclone), 100μM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol $5.5x10^{-5}$M (Gibco), and 10mM Hepes (Gibco). To activate the cells, we used PWM at 5μg/ml or anti-CD40 (Pharmingen) at approximately 10μg/ml and IL-4 at 5-10ng/ml. Cells were harvested for RNA preparation at 24,48 and 72 hours.

To prepare the primary and secondary Th1/Th2 and Tr1 cells, six-well Falcon plates were coated overnight with 10μg/ml anti-CD28 (Pharmingen) and 2μg/ml OKT3 (ATCC), and then washed twice with PBS. Umbilical cord blood CD4 lymphocytes (Poietic Systems, German Town, MD) were cultured at 10^5-10^6cells/ml in DMEM 5% FCS (Hyclone), 100μM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol $5.5x10^{-5}$M (Gibco), 10mM Hepes (Gibco) and IL-2 (4ng/ml). IL-12 (5ng/ml) and anti-IL4 (1μg/ml) were used to direct to Th1, while IL-4 (5ng/ml) and anti-IFN gamma (1μg/ml) were used to direct to Th2 and IL-10 at 5ng/ml was used to direct to Tr1. After 4-5 days, the activated Th1, Th2 and Tr1 lymphocytes were washed once in DMEM and expanded for 4-7 days in DMEM 5% FCS (Hyclone), 100μM non essential amino acids (Gibco), 1mM sodium pyruvate

(Gibco), mercaptoethanol $5.5x10^{-5}$M (Gibco), 10mM Hepes (Gibco) and IL-2 (1ng/ml). Following this, the activated Th1, Th2 and Tr1 lymphocytes were re-stimulated for 5 days with anti-CD28/OKT3 and cytokines as described above, but with the addition of anti-CD95L (1μg/ml) to prevent apoptosis. After 4-5 days, the Th1, Th2 and Tr1 lymphocytes were washed and then expanded again with IL-2 for 4-7 days. Activated Th1 and Th2 lymphocytes were maintained in this way for a maximum of three cycles. RNA was prepared from primary and secondary Th1, Th2 and Tr1 after 6 and 24 hours following the second and third activations with plate bound anti-CD3 and anti-CD28 mAbs and 4 days into the second and third expansion cultures in Interleukin 2.

The following leukocyte cells lines were obtained from the ATCC: Ramos, EOL-1, KU-812. EOL cells were further differentiated by culture in 0.1mM dbcAMP at $5x10^5$cells/ml for 8 days, changing the media every 3 days and adjusting the cell concentration to $5x10^5$cells/ml. For the culture of these cells, we used DMEM or RPMI (as recommended by the ATCC), with the addition of 5% FCS (Hyclone), 100μM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol $5.5x10^{-5}$M (Gibco), 10mM Hepes (Gibco). RNA was either prepared from resting cells or cells activated with PMA at 10ng/ml and ionomycin at 1μg/ml for 6 and 14 hours. Keratinocyte line CCD106 and an airway epithelial tumor line NCI-H292 were also obtained from the ATCC. Both were cultured in DMEM 5% FCS (Hyclone), 100μM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol $5.5x10^{-5}$M (Gibco), and 10mM Hepes (Gibco). CCD1106 cells were activated for 6 and 14 hours with approximately 5 ng/ml TNF alpha and 1ng/ml IL-1 beta, while NCI-H292 cells were activated for 6 and 14 hours with the following cytokines: 5ng/ml IL-4, 5ng/ml IL-9, 5ng/ml IL-13 and 25ng/ml IFN gamma.

For these cell lines and blood cells, RNA was prepared by lysing approximately 10^7cells/ml using Trizol (Gibco BRL). Briefly, 1/10 volume of bromochloropropane (Molecular Research Corporation) was added to the RNA sample, vortexed and after 10 minutes at room temperature, the tubes were spun at 14,000 rpm in a Sorvall SS34 rotor. The aqueous phase was removed and placed in a 15ml Falcon Tube. An equal volume of isopropanol was added and left at -20°C overnight. The precipitated RNA was spun down at 9,000 rpm for 15 min in a Sorvall SS34 rotor and washed in 70% ethanol. The pellet was redissolved in 300μl of RNAse-free water and 35μl buffer (Promega) 5μl DTT, 7μl RNAsin and 8μl DNAse were added. The tube was incubated at 37°C for 30 minutes to remove contaminating genomic DNA, extracted once with phenol chloroform and re-precipitated with

1/10 volume of 3M sodium acetate and 2 volumes of 100% ethanol. The RNA was spun down and placed in RNAse free water. RNA was stored at -80°C.

AI_comprehensive panel_v1.0

The plates for AI_comprehensive panel_v1.0 include two control wells and 89 test samples comprised of cDNA isolated from surgical and postmortem human tissues obtained from the Backus Hospital and Clinomics (Frederick, MD). Total RNA was extracted from tissue samples from the Backus Hospital in the Facility at CuraGen. Total RNA from other tissues was obtained from Clinomics.

Joint tissues including synovial fluid, synovium, bone and cartilage were obtained from patients undergoing total knee or hip replacement surgery at the Backus Hospital. Tissue samples were immediately snap frozen in liquid nitrogen to ensure that isolated RNA was of optimal quality and not degraded. Additional samples of osteoarthritis and rheumatoid arthritis joint tissues were obtained from Clinomics. Normal control tissues were supplied by Clinomics and were obtained during autopsy of trauma victims.

Surgical specimens of psoriatic tissues and adjacent matched tissues were provided as total RNA by Clinomics. Two male and two female patients were selected between the ages of 25 and 47. None of the patients were taking prescription drugs at the time samples were isolated.

Surgical specimens of diseased colon from patients with ulcerative colitis and Crohns disease and adjacent matched tissues were obtained from Clinomics. Bowel tissue from three female and three male Crohn's patients between the ages of 41-69 were used. Two patients were not on prescription medication while the others were taking dexamethasone, phenobarbital, or tylenol. Ulcerative colitis tissue was from three male and four female patients. Four of the patients were taking lebvid and two were on phenobarbital.

Total RNA from post mortem lung tissue from trauma victims with no disease or with emphysema, asthma or COPD was purchased from Clinomics. Emphysema patients ranged in age from 40-70 and all were smokers, this age range was chosen to focus on patients with cigarette-linked emphysema and to avoid those patients with alpha-1anti-trypsin deficiencies. Asthma patients ranged in age from 36-75, and excluded smokers to prevent those patients that could also have COPD. COPD patients ranged in age from 35-80 and included both smokers and non-smokers. Most patients were taking corticosteroids, and bronchodilators.

In the labels employed to identify tissues in the AI_comprehensive panel_v1.0 panel, the following abbreviations are used:

AI = Autoimmunity

Syn = Synovial

Normal = No apparent disease

Rep22 /Rep20 = individual patients

RA = Rheumatoid arthritis

Backus = From Backus Hospital

OA = Osteoarthritis

(SS) (BA) (MF) = Individual patients

Adj = Adjacent tissue

Match control = adjacent tissues

-M = Male

-F = Female

COPD = Chronic obstructive pulmonary disease

Panels 5D and 5I

The plates for Panel 5D and 5I include two control wells and a variety of cDNAs isolated from human tissues and cell lines with an emphasis on metabolic diseases. Metabolic tissues were obtained from patients enrolled in the Gestational Diabetes study. Cells were obtained during different stages in the differentiation of adipocytes from human mesenchymal stem cells. Human pancreatic islets were also obtained.

In the Gestational Diabetes study subjects are young (18 - 40 years), otherwise healthy women with and without gestational diabetes undergoing routine (elective) Caesarean section. After delivery of the infant, when the surgical incisions were being repaired/closed, the obstetrician removed a small sample.

Patient 2: Diabetic Hispanic, overweight, not on insulin

Patient 7-9: Nondiabetic Caucasian and obese (BMI>30)

Patient 10: Diabetic Hispanic, overweight, on insulin

Patient 11: Nondiabetic African American and overweight

Patient 12: Diabetic Hispanic on insulin

Adipocyte differentiation was induced in donor progenitor cells obtained from Osirus (a division of Clonetics/BioWhittaker) in triplicate, except for Donor 3U which had only two replicates. Scientists at Clonetics isolated, grew and differentiated human mesenchymal stem cells (HuMSCs) for CuraGen based on the published protocol found in Mark F. Pittenger, et al., Multilineage Potential of Adult Human Mesenchymal Stem Cells Science Apr 2 1999:

143-147. Clonetics provided Trizol lysates or frozen pellets suitable for mRNA isolation and ds cDNA production. A general description of each donor is as follows:

Donor 2 and 3 U: Mesenchymal Stem cells, Undifferentiated Adipose

Donor 2 and 3 AM: Adipose, AdiposeMidway Differentiated

Donor 2 and 3 AD: Adipose, Adipose Differentiated

Human cell lines were generally obtained from ATCC (American Type Culture Collection), NCI or the German tumor cell bank and fall into the following tissue groups: kidney proximal convoluted tubule, uterine smooth muscle cells, small intestine, liver HepG2 cancer cells, heart primary stromal cells, and adrenal cortical adenoma cells. These cells are all cultured under standard recommended conditions and RNA extracted using the standard procedures. All samples were processed at CuraGen to produce single stranded cDNA.

Panel 5I contains all samples previously described with the addition of pancreatic islets from a 58 year old female patient obtained from the Diabetes Research Institute at the University of Miami School of Medicine. Islet tissue was processed to total RNA at an outside source and delivered to CuraGen for addition to panel 5I.

In the labels employed to identify tissues in the 5D and 5I panels, the following abbreviations are used:

GO Adipose = Greater Omentum Adipose

SK = Skeletal Muscle

UT = Uterus

PL = Placenta

AD = Adipose Differentiated

AM = Adipose Midway Differentiated

U = Undifferentiated Stem Cells

Panel CNSD.01

The plates for Panel CNSD.01 include two control wells and 94 test samples comprised of cDNA isolated from postmortem human brain tissue obtained from the Harvard Brain Tissue Resource Center. Brains are removed from calvaria of donors between 4 and 24 hours after death, sectioned by neuroanatomists, and frozen at -80°C in liquid nitrogen vapor. All brains are sectioned and examined by neuropathologists to confirm diagnoses with clear associated neuropathology.

Disease diagnoses are taken from patient records. The panel contains two brains from each of the following diagnoses: Alzheimer's disease, Parkinson's disease, Huntington's disease, Progressive Supernuclear Palsy, Depression, and "Normal controls". Within each of these brains, the following regions are represented: cingulate gyrus, temporal pole, globus palladus, substantia nigra, Brodman Area 4 (primary motor strip), Brodman Area 7 (parietal cortex), Brodman Area 9 (prefrontal cortex), and Brodman area 17 (occipital cortex). Not all brain regions are represented in all cases; e.g., Huntington's disease is characterized in part by neurodegeneration in the globus palladus, thus this region is impossible to obtain from confirmed Huntington's cases. Likewise Parkinson's disease is characterized by degeneration of the substantia nigra making this region more difficult to obtain. Normal control brains were examined for neuropathology and found to be free of any pathology consistent with neurodegeneration.

In the labels employed to identify tissues in the CNS panel, the following abbreviations are used:

PSP = Progressive supranuclear palsy

Sub Nigra = Substantia nigra

Glob Palladus= Globus palladus

Temp Pole = Temporal pole

Cing Gyr = Cingulate gyrus

BA 4 = Brodman Area 4

Panel CNS_Neurodegeneration_V1.0

The plates for Panel CNS_Neurodegeneration_V1.0 include two control wells and 47 test samples comprised of cDNA isolated from postmortem human brain tissue obtained from the Harvard Brain Tissue Resource Center (McLean Hospital) and the Human Brain and Spinal Fluid Resource Center (VA Greater Los Angeles Healthcare System). Brains are removed from calvaria of donors between 4 and 24 hours after death, sectioned by neuroanatomists, and frozen at -80°C in liquid nitrogen vapor. All brains are sectioned and examined by neuropathologists to confirm diagnoses with clear associated neuropathology.

Disease diagnoses are taken from patient records. The panel contains six brains from Alzheimer's disease (AD) patients, and eight brains from "Normal controls" who showed no evidence of dementia prior to death. The eight normal control brains are divided into two categories: Controls with no dementia and no Alzheimer's like pathology (Controls) and controls with no dementia but evidence of severe Alzheimer's like pathology, (specifically

senile plaque load rated as level 3 on a scale of 0-3; 0 = no evidence of plaques, 3 = severe AD senile plaque load). Within each of these brains, the following regions are represented: hippocampus, temporal cortex (Brodman Area 21), parietal cortex (Brodman area 7), and occipital cortex (Brodman area 17). These regions were chosen to encompass all levels of neurodegeneration in AD. The hippocampus is a region of early and severe neuronal loss in AD; the temporal cortex is known to show neurodegeneration in AD after the hippocampus; the parietal cortex shows moderate neuronal death in the late stages of the disease; the occipital cortex is spared in AD and therefore acts as a "control" region within AD patients. Not all brain regions are represented in all cases.

In the labels employed to identify tissues in the CNS_Neurodegeneration_V1.0 panel, the following abbreviations are used:

AD = Alzheimer's disease brain; patient was demented and showed AD-like pathology upon autopsy

Control = Control brains; patient not demented, showing no neuropathology

Control (Path) = Control brains; pateint not demented but showing sever AD-like pathology

SupTemporal Ctx = Superior Temporal Cortex

Inf Temporal Ctx = Inferior Temporal Cortex

A. NOV1 CG50377-01/ 146642892 and CG50377-02: Cub and Sushi Domain-Containing Protein

Expression of gene CG50377-01 and variant CG50377-02 was assessed using the primer-probe sets Ag2420, Ag169, Ag65 and Ag575, described in Tables 13AA, 13AB, 13AC and 13AD. Results of the RTQ-PCR runs are shown in Tables 13AE, 13AF, 13AG, 13AH, 13AI, 13AJ, 13AK and 13AL.

Table 13AA. Probe Name Ag2420

Primers	Sequences	Length	Start Position
Forward	5'-ctgcacttggctggaactta-3' (SEQ ID NO: 113)	20	9465
Probe	TET-5'-tttcatctcctactccaggtgtacca-3'-TAMRA(SEQ ID NO: 114)	26	9498
Reverse	5'-atctccacaggccctgtaat-3'(SEQ ID NO: 115)	20	9525

Table 13AB. Probe Name Ag169

Primers	Sequences	Length	Start Position
Forward	5'-ccagccatgctcagagtgact-3' (SEQ ID NO: 116)	21	9384
Probe	TET-5'-ttgccaacagcaaggtcaatgccac-3'-TAMRA(SEQ ID NO: 117)	25	9415
Reverse	5'-cgccactgtggtcgatcat-3'(SEQ ID NO: 118)	19	9441

Table 13AC. Probe Name Ag65

Primers	Sequences	Length	Start Position
Forward	5'-ccacagtttgggatacagaacaatt-3' (SEQ ID NO: 119)	25	8923
Probe	TET-5'-actgtgcttccaacctggtagccctga-3'-TAMRA (SEQ ID NO: 120)	27	8949
Reverse	5'-agccttttgacaacggaagag-3' (SEQ ID NO: 121)	22	8977

Table 13AD. Probe Name Ag575

Primers	Sequences	Length	Start Position
Forward	5'-aagctggagtatcaggcctatga-3' (SEQ ID NO: 122)	23	5485
Probe	TET-5'-agagtgcccagacccagagcccttt-3'-TAMRA (SEQ ID NO: 123)	25	5514
Reverse	5'-ctcccctcacaatgccattg-3' (SEQ ID NO: 124)	20	5541

Table 13AE. CNS_neurodegeneration_v1.0

Tissue Name	Rel. Exp.(%) Ag2420, Run 208714879	Tissue Name	Rel. Exp.(%) Ag2420, Run 208714879
AD 1 Hippo	8.4	Control (Path) 3 Temporal Ctx	1.8
AD 2 Hippo	14.9	Control (Path) 4 Temporal Ctx	15.7
AD 3 Hippo	1.8	AD 1 Occipital Ctx	11.0
AD 4 Hippo	3.0	AD 2 Occipital Ctx (Missing)	0.0
AD 5 Hippo	**100.0**	AD 3 Occipital Ctx	1.9
AD 6 Hippo	32.3	AD 4 Occipital Ctx	9.1
Control 2 Hippo	11.1	AD 5 Occipital Ctx	17.1
Control 4 Hippo	3.3	AD 5 Occipital Ctx	24.7
Control (Path) 3 Hippo	2.6	Control 1 Occipital Ctx	1.7
AD 1 Temporal Ctx	5.7	Control 2 Occipital Ctx	49.0
AD 2 Temporal Ctx	10.5	Control 3 Occipital Ctx	11.2
AD 3 Temporal Ctx	2.8	Control 4 Occipital Ctx	1.2
AD 4 Temporal Ctx	10.1	Control (Path) 1 Occipital Ctx	48.6
AD 5 Inf Temporal Ctx	36.3	Control (Path) 2 Occipital Ctx	8.6
AD 5 Sup Temporal Ctx	33.2	Control (Path) 3 Occipital Ctx	1.2
AD 6 Inf Temporal Ctx	33.9	Control (Path) 4 Occipital Ctx	9.7
AD 6 Sup Temporal Ctx	35.4	Control 1 Parietal Ctx	0.8
Control 1 Temporal Ctx	3.1	Control 2 Parietal Ctx	14.9

Control 2 Temporal Ctx	16.4	Control 3 Parietal Ctx	9.2
Control 3 Temporal Ctx	8.0	Control (Path) 1 Parietal Ctx	39.5
Control 3 Temporal Ctx	2.5	Control (Path) 2 Parietal Ctx	16.5
Control (Path) 1 Temporal Ctx	31.9	Control (Path) 3 Parietal Ctx	0.7
Control (Path) 2 Temporal Ctx	23.3	Control (Path) 4 Parietal Ctx	38.7

Table 13AF. Panel 1

Tissue Name	Rel. Exp.(%) Ag169, Run 87590884	Rel. Exp.(%) Ag169, Run 87591554	Rel. Exp.(%) Ag65, Run 87352491	Tissue Name	Rel. Exp.(%) Ag169, Run 87590884	Rel. Exp.(%) Ag169, Run 87591554	Rel. Exp.(%) Ag65, Run 87352491
Endothelial cells	0.0	0.0	0.0	Renal ca. 786-0	0.0	0.0	0.0
Endothelial cells (treated)	0.0	0.0	0.0	Renal ca. A498	0.0	0.0	0.0
Pancreas	0.0	0.0	0.0	Renal ca. RXF 393	0.0	0.0	0.0
Pancreatic ca. CAPAN 2	0.0	0.0	0.0	Renal ca. ACHN	0.0	0.0	0.0
Adrenal gland	0.0	0.0	0.0	Renal ca. UO-31	0.0	0.0	0.0
Thyroid	0.0	0.0	0.0	Renal ca. TK-10	0.0	0.0	0.0
Salivary gland	0.0	0.0	0.0	Liver	0.0	0.0	0.0
Pituitary gland	0.0	0.0	0.0	Liver (fetal)	0.0	0.0	0.0
Brain (fetal)	46.7	**100.0**	**100.0**	Liver ca. (hepatoblast) HepG2	0.0	0.0	0.0
Brain (whole)	3.3	0.0	24.5	Lung	0.0	0.0	0.0
Brain (amygdala)	0.0	0.0	11.1	Lung (fetal)	0.0	0.0	0.0
Brain (cerebellum)	**100.0**	41.5	22.4	Lung ca. (small cell) LX-1	0.0	0.0	0.0
Brain (hippocampus)	0.0	0.0	22.8	Lung ca. (small cell) NCI-H69	0.0	0.0	0.0
Brain (substantia nigra)	0.0	0.0	8.5	Lung ca. (s.cell var.) SHP-77	0.0	0.0	0.0
Brain	0.0	0.0	2.5	Lung ca.	0.0	0.0	0.0

(thalamus)				(large cell)NCI-H460			
Brain (hypothalamus)	0.0	0.0	0.0	Lung ca. (non-sm. cell) A549	0.0	0.0	0.0
Spinal cord	0.0	0.0	2.2	Lung ca. (non-s.cell) NCI-H23	0.0	0.0	0.0
glio/astro U87-MG	34.4	0.5	29.9	Lung ca. (non-s.cell) HOP-62	0.0	0.0	0.0
glio/astro U-118-MG	0.0	0.0	0.0	Lung ca. (non-s.cl) NCI-H522	0.0	0.0	0.0
astrocytoma SW1783	0.0	0.0	0.9	Lung ca. (squam.) SW 900	0.0	0.0	0.0
neuro*; met SK-N-AS	0.0	0.0	0.0	Lung ca. (squam.) NCI-H596	0.0	0.0	0.0
astrocytoma SF-539	0.0	0.0	0.0	Mammary gland	0.0	0.0	0.0
astrocytoma SNB-75	0.0	0.0	0.0	Breast ca.* (pl.ef) MCF-7	0.0	0.0	0.0
glioma SNB-19	0.0	0.0	0.0	Breast ca.* (pl.ef) MDA-MB-231	0.0	0.0	0.0
glioma U251	0.0	0.0	0.1	Breast ca.* (pl. ef) T47D	0.0	0.0	0.0
glioma SF-295	0.0	0.0	0.9	Breast ca. BT-549	0.0	0.0	0.0
Heart	0.0	0.0	0.0	Breast ca. MDA-N	0.0	0.0	0.0
Skeletal muscle	0.0	0.0	0.0	Ovary	0.0	0.0	0.0
Bone marrow	0.0	0.0	0.0	Ovarian ca. OVCAR-3	0.0	0.0	0.0
Thymus	0.0	0.0	0.0	Ovarian ca. OVCAR-4	0.0	0.0	0.0
Spleen	0.0	0.0	0.0	Ovarian ca. OVCAR-5	0.0	0.0	0.0
Lymph node	0.0	0.0	0.0	Ovarian ca. OVCAR-8	0.0	0.0	0.0
Colon	0.0	0.0	0.0	Ovarian ca.	0.0	0.0	0.0

(ascending)				IGROV-1			
Stomach	0.0	0.0	0.0	Ovarian ca. (ascites) SK-OV-3	0.0	0.0	0.0
Small intestine	0.0	0.0	0.0	Uterus	0.0	0.0	0.0
Colon ca. SW480	0.0	0.0	0.0	Placenta	0.0	0.0	0.0
Colon ca.* SW620 (SW480 met)	0.0	0.0	0.0	Prostate	0.0	0.0	0.0
Colon ca. HT29	0.0	0.0	0.0	Prostate ca.* (bone met) PC-3	0.0	0.0	0.0
Colon ca. HCT-116	0.0	0.0	0.0	Testis	0.0	0.0	0.5
Colon ca. CaCo-2	0.0	0.0	0.0	Melanoma Hs688(A).T	0.0	0.0	0.0
Colon ca. HCT-15	0.0	0.0	0.0	Melanoma* (met) Hs688(B).T	0.0	0.0	0.0
Colon ca. HCC-2998	0.0	0.0	0.0	Melanoma UACC-62	0.0	0.0	0.0
Gastric ca. (liver met) NCI-N87	0.0	0.0	0.0	Melanoma M14	0.0	0.0	0.0
Bladder	0.0	0.0	0.0	Melanoma LOX IMVI	0.0	0.0	0.0
Trachea	0.0	0.0	0.0	Melanoma* (met) SK-MEL-5	0.0	0.0	0.0
Kidney	0.0	0.0	0.0	Melanoma SK-MEL-28	0.0	0.0	0.0
Kidney (fetal)	0.0	0.0	0.0				

Table 13AG. Panel 1.1

Tissue Name	Rel. Exp.(%) Ag575, Run 109646812	Tissue Name	Rel. Exp.(%) Ag575, Run 109646812
Adrenal gland	0.4	Renal ca. UO-31	0.0
Bladder	9.8	Renal ca. RXF 393	0.0
Brain (amygdala)	3.7	Liver	0.0
Brain (cerebellum)	18.6	Liver (fetal)	0.0
Brain (hippocampus)	15.9	Liver ca. (hepatoblast) HepG2	0.0
Brain (substantia nigra)	31.9	Lung	0.0
Brain (thalamus)	3.6	Lung (fetal)	0.0
Cerebral Cortex	34.6	Lung ca. (non-s.cell)	0.0

		HOP-62	
Brain (fetal)	69.7	Lung ca. (large cell)NCI-H460	0.0
Brain (whole)	15.6	Lung ca. (non-s.cell) NCI-H23	0.0
glio/astro U-118-MG	1.4	Lung ca. (non-s.cl) NCI-H522	0.8
astrocytoma SF-539	0.0	Lung ca. (non-sm. cell) A549	0.0
astrocytoma SNB-75	0.0	Lung ca. (s.cell var.) SHP-77	0.0
astrocytoma SW1783	11.4	Lung ca. (small cell) LX-1	0.0
glioma U251	2.2	Lung ca. (small cell) NCI-H69	0.0
glioma SF-295	20.6	Lung ca. (squam.) SW 900	0.0
glioma SNB-19	1.9	Lung ca. (squam.) NCI-H596	0.0
glio/astro U87-MG	**100.0**	Lymph node	0.0
neuro*; met SK-N-AS	0.0	Spleen	0.0
Mammary gland	0.0	Thymus	0.0
Breast ca. BT-549	0.0	Ovary	0.0
Breast ca. MDA-N	0.0	Ovarian ca. IGROV-1	0.0
Breast ca.* (pl. ef) T47D	0.0	Ovarian ca. OVCAR-3	0.0
Breast ca.* (pl.ef) MCF-7	0.0	Ovarian ca. OVCAR-4	0.0
Breast ca.* (pl.ef) MDA-MB-231	0.0	Ovarian ca. OVCAR-5	0.0
Small intestine	0.0	Ovarian ca. OVCAR-8	0.0
Colorectal	0.0	Ovarian ca. (ascites) SK-OV-3	0.0
Colon ca. HT29	0.0	Pancreas	0.0
Colon ca. CaCo-2	0.0	Pancreatic ca. CAPAN 2	0.0
Colon ca. HCT-15	0.0	Pituitary gland	0.1
Colon ca. HCT-116	0.0	Placenta	0.0
Colon ca. HCC-2998	0.0	Prostate	0.0
Colon ca. SW480	0.0	Prostate ca.* (bone met) PC-3	0.0
Colon ca.* SW620 (SW480 met)	0.0	Salivary gland	0.0

Stomach	0.1	Trachea	0.0
Gastric ca. (liver met) NCI-N87	0.0	Spinal cord	3.3
Heart	0.1	Testis	0.1
Skeletal muscle (Fetal)	0.1	Thyroid	0.0
Skeletal muscle	0.0	Uterus	0.0
Endothelial cells	0.0	Melanoma M14	0.0
Heart (Fetal)	0.0	Melanoma LOX IMVI	0.0
Kidney	0.0	Melanoma UACC-62	0.0
Kidney (fetal)	0.0	Melanoma SK-MEL-28	0.0
Renal ca. 786-0	0.0	Melanoma* (met) SK-MEL-5	0.0
Renal ca. A498	0.0	Melanoma Hs688(A).T	1.9
Renal ca. ACHN	0.0	Melanoma* (met) Hs688(B).T	1.8
Renal ca. TK-10	0.0		

Table 13AH. Panel 1.2

Tissue Name	Rel. Exp.(%) Ag575, Run 116351999	Tissue Name	Rel. Exp.(%) Ag575, Run 116351999
Endothelial cells	0.1	Renal ca. 786-0	0.0
Heart (Fetal)	0.1	Renal ca. A498	0.0
Pancreas	0.5	Renal ca. RXF 393	0.0
Pancreatic ca. CAPAN 2	0.0	Renal ca. ACHN	0.0
Adrenal gland	1.9	Renal ca. UO-31	0.0
Thyroid	0.3	Renal ca. TK-10	0.0
Salivary gland	0.2	Liver	0.1
Pituitary gland	1.1	Liver (fetal)	0.1
Brain (fetal)	**100.0**	Liver ca. (hepatoblast) HepG2	0.0
Brain (whole)	9.1	Lung	0.0
Brain (amygdala)	7.1	Lung (fetal)	0.0
Brain (cerebellum)	5.3	Lung ca. (small cell) LX-1	0.0
Brain (hippocampus)	10.2	Lung ca. (small cell) NCI-H69	0.0
Brain (thalamus)	1.8	Lung ca. (s.cell var.) SHP-77	0.0
Cerebral Cortex	8.8	Lung ca. (large cell)NCI-H460	0.0

Spinal cord	1.9	Lung ca. (non-sm. cell) A549	0.0
glio/astro U87-MG	44.8	Lung ca. (non-s.cell) NCI-H23	0.0
glio/astro U-118-MG	0.8	Lung ca. (non-s.cell) HOP-62	0.1
astrocytoma SW1783	4.3	Lung ca. (non-s.cl) NCI-H522	1.0
neuro*; met SK-N-AS	0.0	Lung ca. (squam.) SW 900	0.0
astrocytoma SF-539	0.0	Lung ca. (squam.) NCI-H596	0.0
astrocytoma SNB-75	0.0	Mammary gland	0.4
glioma SNB-19	2.0	Breast ca.* (pl.ef) MCF-7	0.0
glioma U251	3.8	Breast ca.* (pl.ef) MDA-MB-231	0.0
glioma SF-295	5.4	Breast ca.* (pl. ef) T47D	0.0
Heart	1.1	Breast ca. BT-549	0.2
Skeletal muscle	0.7	Breast ca. MDA-N	0.0
Bone marrow	0.0	Ovary	0.2
Thymus	0.0	Ovarian ca. OVCAR-3	0.0
Spleen	0.3	Ovarian ca. OVCAR-4	0.0
Lymph node	0.4	Ovarian ca. OVCAR-5	0.0
Colorectal	0.0	Ovarian ca. OVCAR-8	0.0
Stomach	0.4	Ovarian ca. IGROV-1	0.0
Small intestine	0.4	Ovarian ca. (ascites) SK-OV-3	0.0
Colon ca. SW480	0.0	Uterus	0.2
Colon ca.* SW620 (SW480 met)	0.0	Placenta	0.0
Colon ca. HT29	0.0	Prostate	1.0
Colon ca. HCT-116	0.1	Prostate ca.* (bone met) PC-3	0.0
Colon ca. CaCo-2	0.0	Testis	1.9
CC Well to Mod Diff (ODO3866)	0.4	Melanoma Hs688(A).T	1.5
Colon ca. HCC-2998	0.0	Melanoma* (met) Hs688(B).T	0.9
Gastric ca. (liver met)	0.0	Melanoma UACC-62	0.0

NCI-N87			
Bladder	4.0	Melanoma M14	0.0
Trachea	0.1	Melanoma LOX IMVI	0.0
Kidney	0.4	Melanoma* (met) SK-MEL-5	0.0
Kidney (fetal)	1.1		

Table 13AI. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2420, Run 159253002	Tissue Name	Rel. Exp.(%) Ag2420, Run 159253002
Liver adenocarcinoma	0.0	Kidney (fetal)	0.6
Pancreas	0.9	Renal ca. 786-0	0.0
Pancreatic ca. CAPAN 2	0.0	Renal ca. A498	0.2
Adrenal gland	1.1	Renal ca. RXF 393	0.0
Thyroid	0.2	Renal ca. ACHN	0.0
Salivary gland	0.0	Renal ca. UO-31	0.0
Pituitary gland	0.4	Renal ca. TK-10	0.0
Brain (fetal)	**100.0**	Liver	0.0
Brain (whole)	13.6	Liver (fetal)	0.2
Brain (amygdala)	27.4	Liver ca. (hepatoblast) HepG2	0.0
Brain (cerebellum)	3.9	Lung	0.6
Brain (hippocampus)	95.3	Lung (fetal)	0.2
Brain (substantia nigra)	5.0	Lung ca. (small cell) LX-1	0.0
Brain (thalamus)	7.9	Lung ca. (small cell) NCI-H69	0.0
Cerebral Cortex	37.6	Lung ca. (s.cell var.) SHP-77	0.0
Spinal cord	2.5	Lung ca. (large cell)NCI-H460	0.0
glio/astro U87-MG	50.3	Lung ca. (non-sm. cell) A549	0.0
glio/astro U-118-MG	2.7	Lung ca. (non-s.cell) NCI-H23	0.0
astrocytoma SW1783	10.9	Lung ca. (non-s.cell) HOP-62	0.0
neuro*; met SK-N-AS	0.0	Lung ca. (non-s.cl) NCI-H522	0.2
astrocytoma SF-539	0.0	Lung ca. (squam.) SW 900	0.0
astrocytoma SNB-75	0.0	Lung ca. (squam.) NCI-H596	0.0

glioma SNB-19	0.8	Mammary gland	0.4
glioma U251	1.4	Breast ca.* (pl.ef) MCF-7	0.0
glioma SF-295	7.8	Breast ca.* (pl.ef) MDA-MB-231	0.0
Heart (Fetal)	0.0	Breast ca.* (pl. ef) T47D	0.0
Heart	0.2	Breast ca. BT-549	1.3
Skeletal muscle (Fetal)	1.3	Breast ca. MDA-N	0.0
Skeletal muscle	0.0	Ovary	0.5
Bone marrow	0.0	Ovarian ca. OVCAR-3	0.0
Thymus	0.0	Ovarian ca. OVCAR-4	0.0
Spleen	1.2	Ovarian ca. OVCAR-5	0.0
Lymph node	0.2	Ovarian ca. OVCAR-8	0.0
Colorectal	0.0	Ovarian ca. IGROV-1	0.0
Stomach	0.2	Ovarian ca. (ascites) SK-OV-3	0.0
Small intestine	1.7	Uterus	0.0
Colon ca. SW480	0.3	Placenta	0.2
Colon ca.* SW620 (SW480 met)	0.0	Prostate	0.4
Colon ca. HT29	0.0	Prostate ca.* (bone met) PC-3	0.0
Colon ca. HCT-116	0.0	Testis	1.3
Colon ca. CaCo-2	0.0	Melanoma Hs688(A).T	2.4
CC Well to Mod Diff (ODO3866)	1.1	Melanoma* (met) Hs688(B).T	0.3
Colon ca. HCC-2998	0.0	Melanoma UACC-62	0.0
Gastric ca. (liver met) NCI-N87	0.0	Melanoma M14	0.0
Bladder	0.6	Melanoma LOX IMVI	0.0
Trachea	0.2	Melanoma* (met) SK-MEL-5	0.0
Kidney	0.0	Adipose	0.5

Table 13AJ. Panel 2D

Tissue Name	Rel. Exp.(%) Ag2420, Run 159254587	Tissue Name	Rel. Exp.(%) Ag2420, Run 159254587

Normal Colon	10.0	Kidney Margin 8120608	3.3
CC Well to Mod Diff (ODO3866)	11.1	Kidney Cancer 8120613	2.9
CC Margin (ODO3866)	7.3	Kidney Margin 8120614	1.1
CC Gr.2 rectosigmoid (ODO3868)	3.2	Kidney Cancer 9010320	3.1
CC Margin (ODO3868)	1.8	Kidney Margin 9010321	3.8
CC Mod Diff (ODO3920)	4.1	Normal Uterus	0.0
CC Margin (ODO3920)	2.3	Uterine Cancer 064011	1.9
CC Gr.2 ascend colon (ODO3921)	5.2	Normal Thyroid	1.7
CC Margin (ODO3921)	5.0	Thyroid Cancer	1.8
CC from Partial Hepatectomy (ODO4309) Mets	67.4	Thyroid Cancer A302152	5.2
Liver Margin (ODO4309)	0.0	Thyroid Margin A302153	0.0
Colon mets to lung (OD04451-01)	4.5	Normal Breast	1.4
Lung Margin (OD04451-02)	0.0	Breast Cancer	1.6
Normal Prostate 6546-1	5.4	Breast Cancer (OD04590-01)	3.8
Prostate Cancer (OD04410)	11.7	Breast Cancer Mets (OD04590-03)	11.3
Prostate Margin (OD04410)	3.5	Breast Cancer Metastasis	0.0
Prostate Cancer (OD04720-01)	4.7	Breast Cancer	8.0
Prostate Margin (OD04720-02)	4.5	Breast Cancer	3.3
Normal Lung	11.1	Breast Cancer 9100266	3.1
Lung Met to Muscle (ODO4286)	0.0	Breast Margin 9100265	9.5
Muscle Margin (ODO4286)	2.3	Breast Cancer A209073	13.7
Lung Malignant Cancer (OD03126)	33.2	Breast Margin A2090734	0.0
Lung Margin (OD03126)	11.4	Normal Liver	0.0
Lung Cancer (OD04404)	19.3	Liver Cancer	8.5
Lung Margin (OD04404)	2.1	Liver Cancer 1025	0.0

Lung Cancer (OD04565)	15.8	Liver Cancer 1026	12.1
Lung Margin (OD04565)	0.0	Liver Cancer 6004-T	1.7
Lung Cancer (OD04237-01)	13.5	Liver Tissue 6004-N	12.9
Lung Margin (OD04237-02)	1.8	Liver Cancer 6005-T	10.1
Ocular Mel Met to Liver (ODO4310)	0.0	Liver Tissue 6005-N	0.0
Liver Margin (ODO4310)	0.0	Normal Bladder	31.6
Melanoma Metastasis	0.0	Bladder Cancer	10.7
Lung Margin (OD04321)	0.0	Bladder Cancer	**100.0**
Normal Kidney	5.2	Bladder Cancer (OD04718-01)	15.2
Kidney Ca, Nuclear grade 2 (OD04338)	0.0	Bladder Normal Adjacent (OD04718-03)	7.4
Kidney Margin (OD04338)	3.9	Normal Ovary	1.7
Kidney Ca Nuclear grade 1/2 (OD04339)	1.7	Ovarian Cancer	52.1
Kidney Margin (OD04339)	1.0	Ovarian Cancer (OD04768-07)	0.0
Kidney Ca, Clear cell type (OD04340)	16.2	Ovary Margin (OD04768-08)	0.0
Kidney Margin (OD04340)	2.2	Normal Stomach	7.9
Kidney Ca, Nuclear grade 3 (OD04348)	9.4	Gastric Cancer 9060358	0.0
Kidney Margin (OD04348)	0.0	Stomach Margin 9060359	2.5
Kidney Cancer (OD04622-01)	7.0	Gastric Cancer 9060395	15.4
Kidney Margin (OD04622-03)	0.0	Stomach Margin 9060394	2.6
Kidney Cancer (OD04450-01)	0.0	Gastric Cancer 9060397	28.9
Kidney Margin (OD04450-03)	1.8	Stomach Margin 9060396	1.8
Kidney Cancer 8120607	1.7	Gastric Cancer 064005	9.8

Table 13AK. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2420, Run 159255381	Tissue Name	Rel. Exp.(%) Ag2420, Run 159255381
Secondary Th1 act	0.0	HUVEC IL-1beta	0.0

Secondary Th2 act	0.0	HUVEC IFN gamma	0.0
Secondary Tr1 act	0.0	HUVEC TNF alpha + IFN gamma	0.0
Secondary Th1 rest	0.0	HUVEC TNF alpha + IL4	0.0
Secondary Th2 rest	0.0	HUVEC IL-11	0.0
Secondary Tr1 rest	0.0	Lung Microvascular EC none	0.0
Primary Th1 act	0.0	Lung Microvascular EC TNFalpha + IL-1beta	0.0
Primary Th2 act	0.0	Microvascular Dermal EC none	0.0
Primary Tr1 act	0.0	Microsvasular Dermal EC TNFalpha + IL-1beta	0.0
Primary Th1 rest	0.0	Bronchial epithelium TNFalpha + IL1beta	0.0
Primary Th2 rest	0.0	Small airway epithelium none	1.0
Primary Tr1 rest	0.0	Small airway epithelium TNFalpha + IL-1beta	0.0
CD45RA CD4 lymphocyte act	11.3	Coronery artery SMC rest	3.9
CD45RO CD4 lymphocyte act	0.0	Coronery artery SMC TNFalpha + IL-1beta	3.2
CD8 lymphocyte act	0.0	Astrocytes rest	**100.0**
Secondary CD8 lymphocyte rest	0.0	Astrocytes TNFalpha + IL-1beta	32.8
Secondary CD8 lymphocyte act	0.0	KU-812 (Basophil) rest	0.0
CD4 lymphocyte none	0.0	KU-812 (Basophil) PMA/ionomycin	0.0
2ry Th1/Th2/Tr1_anti-CD95 CH11	0.0	CCD1106 (Keratinocytes) none	0.0
LAK cells rest	0.0	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	0.0
LAK cells IL-2	0.0	Liver cirrhosis	0.0
LAK cells IL-2+IL-12	0.0	Lupus kidney	0.0
LAK cells IL-2+IFN gamma	0.0	NCI-H292 none	0.0
LAK cells IL-2+ IL-18	0.0	NCI-H292 IL-4	0.0
LAK cells PMA/ionomycin	0.0	NCI-H292 IL-9	0.0
NK Cells IL-2 rest	0.0	NCI-H292 IL-13	0.0
Two Way MLR 3 day	0.0	NCI-H292 IFN gamma	0.0
Two Way MLR 5 day	0.0	HPAEC none	0.0
Two Way MLR 7 day	0.0	HPAEC TNF alpha + IL-1	0.0

		beta	
PBMC rest	0.0	Lung fibroblast none	36.3
PBMC PWM	0.0	Lung fibroblast TNF alpha + IL-1 beta	4.6
PBMC PHA-L	0.0	Lung fibroblast IL-4	52.9
Ramos (B cell) none	0.0	Lung fibroblast IL-9	78.5
Ramos (B cell) ionomycin	0.0	Lung fibroblast IL-13	37.4
B lymphocytes PWM	0.0	Lung fibroblast IFN gamma	37.6
B lymphocytes CD40L and IL-4	0.0	Dermal fibroblast CCD1070 rest	63.3
EOL-1 dbcAMP	0.0	Dermal fibroblast CCD1070 TNF alpha	27.0
EOL-1 dbcAMP PMA/ionomycin	0.0	Dermal fibroblast CCD1070 IL-1 beta	20.3
Dendritic cells none	0.0	Dermal fibroblast IFN gamma	8.6
Dendritic cells LPS	0.0	Dermal fibroblast IL-4	4.2
Dendritic cells anti-CD40	0.0	IBD Colitis 2	0.0
Monocytes rest	0.0	IBD Crohn's	0.0
Monocytes LPS	0.0	Colon	0.7
Macrophages rest	0.0	Lung	0.8
Macrophages LPS	0.0	Thymus	1.9
HUVEC none	0.0	Kidney	0.0
HUVEC starved	0.0		

Table 13AL. Panel CNS_1

Tissue Name	Rel. Exp.(%) Ag169, Run 171628635	Rel. Exp.(%) Ag2420, Run 171648980	Tissue Name	Rel. Exp.(%) Ag169, Run 171628635	Rel. Exp.(%) Ag2420, Run 171648980
BA4 Control	15.8	11.7	BA17 PSP	49.7	76.8
BA4 Control2	24.7	39.5	BA17 PSP2	36.3	9.5
BA4 Alzheimer's2	6.1	4.3	Sub Nigra Control	23.8	17.6
BA4 Parkinson's	27.0	39.2	Sub Nigra Control2	37.9	7.8
BA4 Parkinson's2	54.0	66.4	Sub Nigra Alzheimer's2	13.2	11.7
BA4 Huntington's	24.7	20.4	Sub Nigra Parkinson's2	37.6	17.3
BA4 Huntington's2	12.8	4.0	Sub Nigra Huntington's	27.4	21.2
BA4 PSP	0.0	0.0	Sub Nigra	17.2	42.3

			Huntington's2		
BA4 PSP2	12.0	4.7	Sub Nigra PSP2	9.3	5.2
BA4 Depression	11.9	4.8	Sub Nigra Depression	9.7	21.9
BA4 Depression2	13.2	0.0	Sub Nigra Depression2	15.0	4.3
BA7 Control	10.8	24.8	Glob Palladus Control	12.1	19.6
BA7 Control2	8.7	15.6	Glob Palladus Control2	42.6	5.6
BA7 Alzheimer's2	8.6	13.9	Glob Palladus Alzheimer's	0.0	7.1
BA7 Parkinson's	33.4	4.7	Glob Palladus Alzheimer's2	4.2	0.0
BA7 Parkinson's2	55.5	37.4	Glob Palladus Parkinson's	59.0	86.5
BA7 Huntington's	35.4	35.8	Glob Palladus Parkinson's2	4.8	5.0
BA7 Huntington's2	**100.0**	37.9	Glob Palladus PSP	8.1	0.0
BA7 PSP	25.3	32.8	Glob Palladus PSP2	0.0	0.0
BA7 PSP2	26.4	22.2	Glob Palladus Depression	1.6	4.5
BA7 Depression	18.4	2.5	Temp Pole Control	0.0	12.9
BA9 Control	11.7	4.4	Temp Pole Control2	32.8	44.4
BA9 Control2	78.5	31.6	Temp Pole Alzheimer's	10.3	0.0
BA9 Alzheimer's	8.2	0.0	Temp Pole Alzheimer's2	4.9	0.0
BA9 Alzheimer's2	7.7	4.7	Temp Pole Parkinson's	22.7	34.4
BA9 Parkinson's	13.6	27.0	Temp Pole Parkinson's2	27.9	18.6
BA9 Parkinson's2	76.8	51.1	Temp Pole Huntington's	39.5	12.3
BA9 Huntington's	60.7	28.1	Temp Pole PSP	0.0	7.7
BA9 Huntington's2	36.9	0.0	Temp Pole PSP2	0.0	0.0
BA9 PSP	24.0	10.2	Temp Pole Depression2	12.7	0.0
BA9 PSP2	5.5	0.0	Cing Gyr	48.6	20.4

			Control		
BA9 Depression	13.5	0.0	Cing Gyr Control2	32.3	39.2
BA9 Depression2	18.7	0.0	Cing Gyr Alzheimer's	0.0	26.1
BA17 Control	92.7	56.6	Cing Gyr Alzheimer's2	22.8	4.8
BA17 Control2	67.4	39.0	Cing Gyr Parkinson's	31.2	31.6
BA17 Alzheimer's2	17.8	5.2	Cing Gyr Parkinson's2	46.7	17.8
BA17 Parkinson's	65.5	23.7	Cing Gyr Huntington's	36.9	33.2
BA17 Parkinson's2	92.7	**100.0**	Cing Gyr Huntington's2	41.5	29.7
BA17 Huntington's	47.0	29.9	Cing Gyr PSP	5.4	18.7
BA17 Huntington's2	33.4	21.6	Cing Gyr PSP2	5.5	0.0
BA17 Depression	34.4	16.7	Cing Gyr Depression	9.2	4.5
BA17 Depression2	27.0	36.3	Cing Gyr Depression2	20.3	24.8

CNS_neurodegeneration_v1.0 Summary: Ag2420 Panel CNS_Neurodegeneration does not show any difference in the expression of this gene between the postmortem brains of controls or Alzheimer's disease patients. This panel does, however, confirm the expression of this gene at moderate to high levels in the brains of an independent group of patients. See Panel 1.3d for discussion of utility in the central nervous system.

Panel 1 Summary: Ag65/Ag169 Three experiments with two different probe and primer sets show expression of this gene to be specific to normal brain derived tissue. In addition, there appears to be expression associated with a sample derived from a brain cancer cell line. Thus, the expression of this gene could be used to distinguish these brain derived tissues from other samples in the panel. Moreover, therapeutic modulation of this gene, through the use of antibodies, small molecule drugs or protein therapeutics might be of benefit in the treatment of brain cancer.

Panels 1.1 and 1.2 Summary: Ag575 Expression of this gene appears to be restricted to normal brain derived tissue. In addition, there appears to be expression associated with a number of samples derived from brain cancer cell lines, with highest expression seen in the brain cancer cell line U87-MG (CT=23.5). Thus, the expression of this gene could be used to distinguish these brain derived tissues from other samples in the panel. Moreover, therapeutic modulation of this gene, through the use of antibodies, small molecule drugs or protein therapeutics might be of benefit in the treatment of brain cancer.

This gene also has moderate levels of expression in a number of metabolic tissues including adrenal, pituitary, heart, and fetal skeletal muscle. Thus, this gene product may be important for the pathogenesis, diagnosis and/or treatment of metabolic disease, including obesity. Furthermore, this gene is expressed at higher levels in fetal skeletal muscle (CT=34.2) than in adult skeletal muscle (CT=37.7). Thus, expression of this gene could be used to differentiate

between adult and fetal sources of this tissue. In addition, the higher levels of expression of the gene in fetal skeletal muscle suggests that the gene product could be used to restore muscle mass or function in the adult.

Panel 1.3D Summary: Ag2420 Expression of thie gene appears to be restricted to normal brain derived tissue, with highest expression seen in the fetal brain (CT=29.8). In addition, there apears to be expression associated with a number of samples derived from brain cancer cell lines. Thus, the expression of this gene could be used to distinguish these brain derived tissues from other samples in the panel. Moreover, therepeutic modulation of this gene, through the use of antibodies, small molecule drugs or protein therapeutics might be of benefit in the treatment of brain cancer.

This gene represents a novel protein containing CUB and sushi domains. Its expression profile is highly brain-preferential; levels in the CNS appear 10-fold greater than in other tissues. At least one brain-specific protein containing CUB and sushi domains has been linked to seizures, and shows differential expression in response to pentylentetrazole. This protein is therefore a drug target for the treatment of epilepsy or any seizure disorder.

References:

Shimizu-Nishikawa K, Kajiwara K, Kimura M, Katsuki M, Sugaya E. Cloning and expression of SEZ-6, a brain-specific and seizure-related cDNA. Brain Res Mol Brain Res 1995 Feb;28(2):201-10

To clarify the molecular mechanism of neuronal bursting activity of seizures, we have constructed a cDNA library from mouse cerebrum cortex-derived cells treated with pentylentetrazole (PTZ), one of the convulsant drugs. Using a differential screening technique, several cDNA clones whose expressions change with PTZ-treatment were obtained. Among these clones, SEZ-6 was characterized by increased expression with PTZ. Detailed northern analysis showed that expression of SEZ-6 was limited to the brain and increased by the administration of PTZ not only in in vitro cultured cells but also in vivo. Analysis of SEZ-6 cDNA revealed multiple motifs, including typical signal sequence, threonine-rich domain, five copies of short consensus repeats (SCRs) or sushi domain (complement C3b/C4b binding site), two repeated sequences which were partially similar to the CUB domain or complement C1r/s-like repeat, one transmembrane domain and a short cytoplasmic segment in the C-terminal region. Although many proteins with multiple SCRs or CUB domains other than complement-related proteins have been found, this is the first report about a brain-specific cDNA which encodes membrane protein with both SCRs and CUB domain-like segments. Based on these findings, it is evident that SEZ-6 encodes a novel type of protein which may be related to seizure.

Panel 2D Summary: The expression of this gene in panel 2D appears to be highest in a sample derived from a bladder cancer. Further the expression of thie gene appears fairly selective for certian tissues, more specifically, gastric cancer, ovarian cancer, bladder cancer and lung cancer. Thus, the expression of this gene could be used to distinguish these samples for other samples in the panel. Moreover, therapeutic modulation of this gene, through the use of antibodies, small molecule drugs or protein therapeutics might be of benefit in the treatment of these cancer types.

Panel 4D Summary: Ag2420 This gene encodes a cub-domain and sushi-domain containing single-pass membrane protein and is expressed at a moderate level (CT=32.21) in TNF-alpha + IL-1-beta-stimulated astrocytes and at a higher level (CT= 30.6) in resting astrocytes. This gene is also expressed at moderate to low levels (CT=30-34) in resting and cytokine-stimulated lung fibroblasts and dermal fibroblasts. The isolated extracellular domain of the protein encoded by this gene may be useful as a therapeutic protein to reduce or eliminate the symptoms of multiple sclerosis, chronic obstructive pulmonary disease, asthma, or

emphysema, and psoriasis. Furthermore, agonist or antagonist antibodies that stimulate or inhibit the function of this gene may also be useful as therapeutics to reduce or eliminate the symptoms of multiple sclerosis, chronic obstructive pulmonary disease, asthma, or emphysema, and psoriasis.

Panel CNS_1 Summary: Ag169/Ag2420 This panel confirms the expression of this CUB and Sushi domain protein in the adult CNS. See Panel 1.3d for a discussion of utility in the central nervous system.

B. NOV4 (SC70504370_A/CG59253-01 and CG59253-02 and CG59253-05 and CG59253-06 and CG59253-07 and CG59253-08)

Expression of gene SC70504370_A and variants CG59253-02 and CG59253-05 and CG59253-06 and CG59253-07 and CG59253-08 was assessed using the primer-probe sets Ag1492 and Ag2441, described in Tables 14BA and 14BB. Results of the RTQ-PCR runs are shown in Tables 14BC, 14BD, 14BE, 14BF, 14BG and 14BH.

Table 14BA. Probe Name Ag1492

Primers	Sequences	Length	Start Position
Forward	5'-ctgaagctggcatggtacttaa-3' (SEQ ID NO: 125)	22	1373
Probe	TET-5'-cagtcctttctctttgaacgacagcg-3'-TAMRA (SEQ ID NO: 126)	26	1410
Reverse	5'-ttgtaggcttcaatctcttcca-3' (SEQ ID NO: 127)	22	1442

Table 14BB. Probe Name Ag2441

Primers	Sequences	Length	Start Position
Forward	5'-tgctatgaaaggcaagcataa-3' (SEQ ID NO: 128)	21	369
Probe	TET-5'-tgaatgccacaactttatcaaagtatttg-3'-TAMRA (SEQ ID NO: 129)	29	393
Reverse	5'-aaaaccatctcatcgtttcttg-3' (SEQ ID NO: 130)	22	425

Table 14BC. CNS_neurodegeneration_v1.0

Tissue Name	Rel. Exp.(%) Ag1492, Run 207567462	Rel. Exp.(%) Ag2441, Run 208272964	Rel. Exp.(%) Ag2441, Run 228397027	Tissue Name	Rel. Exp.(%) Ag1492, Run 207567462	Rel. Exp.(%) Ag2441, Run 208272964	Rel. Exp.(%) Ag2441, Run 228397027
AD 1 Hippo	8.4	0.0	7.3	Control (Path) 3 Temporal Ctx	4.0	0.0	2.6
AD 2 Hippo	18.3	0.1	17.4	Control (Path) 4 Temporal Ctx	23.7	61.6	16.4
AD 3 Hippo	4.3	0.0	2.7	AD 1 Occipital Ctx	19.9	0.0	12.7
AD 4 Hippo	6.3	0.0	2.4	AD 2 Occipital Ctx (Missing)	0.0	45.4	0.0

AD 5 Hippo	**100.0**	29.9	**100.0**	AD 3 Occipital Ctx	5.7	0.0	2.8
AD 6 Hippo	28.5	36.9	27.9	AD 4 Occipital Ctx	20.0	0.0	16.0
Control 2 Hippo	23.0	0.1	21.8	AD 5 Occipital Ctx	34.4	**100.0**	49.0
Control 4 Hippo	8.3	0.0	6.8	AD 5 Occipital Ctx	29.1	51.1	26.6
Control (Path) 3 Hippo	4.7	0.0	2.7	Control 1 Occipital Ctx	3.7	0.0	2.4
AD 1 Temporal Ctx	11.6	0.0	8.0	Control 2 Occipital Ctx	65.1	0.3	99.3
AD 2 Temporal Ctx	21.0	0.1	20.6	Control 3 Occipital Ctx	21.6	0.1	11.6
AD 3 Temporal Ctx	4.5	0.0	2.2	Control 4 Occipital Ctx	5.9	0.0	4.8
AD 4 Temporal Ctx	18.3	0.1	17.6	Control (Path) 1 Occipital Ctx	74.7	0.3	79.0
AD 5 Inf Temporal Ctx	72.2	27.5	79.6	Control (Path) 2 Occipital Ctx	16.0	0.0	9.3
AD 5 Sup Temporal Ctx	26.1	61.6	24.0	Control (Path) 3 Occipital Ctx	3.2	0.0	1.8
AD 6 Inf Temporal Ctx	27.9	0.0	34.4	Control (Path) 4 Occipital Ctx	18.7	39.8	10.4
AD 6 Sup Temporal Ctx	32.8	21.3	39.2	Control 1 Parietal Ctx	7.3	0.0	5.8
Control 1 Temporal Ctx	8.2	0.0	5.6	Control 2 Parietal Ctx	28.3	90.1	26.1
Control 2 Temporal	27.9	0.1	42.3	Control 3 Parietal	16.3	0.1	12.9

Ctx				Ctx			
Control 3 Temporal Ctx	11.1	0.0	9.3	Control (Path) 1 Parietal Ctx	53.6	0.3	74.2
Control 3 Temporal Ctx	7.8	0.0	3.9	Control (Path) 2 Parietal Ctx	21.0	0.1	17.6
Control (Path) 1 Temporal Ctx	33.4	0.2	40.3	Control (Path) 3 Parietal Ctx	4.2	0.0	2.8
Control (Path) 2 Temporal Ctx	25.0	0.1	21.6	Control (Path) 4 Parietal Ctx	33.9	75.3	31.0

Table 14BD. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag1492, Run 165529502	Rel. Exp.(%) Ag2441, Run 159616039	Rel. Exp.(%) Ag2441, Run 165534561	Tissue Name	Rel. Exp.(%) Ag1492, Run 165529502	Rel. Exp.(%) Ag2441, Run 159616039	Rel. Exp.(%) Ag2441, Run 165534561
Liver adenocarcinoma	0.0	0.0	0.0	Kidney (fetal)	14.9	7.8	12.2
Pancreas	4.5	1.4	4.5	Renal ca. 786-0	3.9	1.8	1.2
Pancreatic ca. CAPAN 2	0.0	0.0	0.0	Renal ca. A498	0.6	0.3	0.0
Adrenal gland	2.8	0.8	2.5	Renal ca. RXF 393	9.8	2.2	6.8
Thyroid	4.9	3.3	2.1	Renal ca. ACHN	0.0	0.0	0.0
Salivary gland	2.0	1.1	2.3	Renal ca. UO-31	0.2	0.2	0.7
Pituitary gland	9.2	6.6	2.9	Renal ca. TK-10	0.0	0.0	0.0
Brain (fetal)	44.4	12.1	26.4	Liver	4.4	0.9	2.9
Brain (whole)	**100.0**	20.0	81.2	Liver (fetal)	4.4	1.3	3.1
Brain (amygdala)	27.7	16.8	25.5	Liver ca. (hepatoblast) HepG2	0.0	0.0	0.0
Brain (cerebellum)	42.3	8.8	27.2	Lung	5.0	11.4	4.4
Brain (hippocampus)	50.0	77.9	26.2	Lung (fetal)	7.3	7.4	13.5

Brain (substantia nigra)	42.9	7.6	24.8	Lung ca. (small cell) LX-1	0.0	0.0	0.0
Brain (thalamus)	52.1	15.3	30.1	Lung ca. (small cell) NCI-H69	4.0	23.0	18.4
Cerebral Cortex	43.2	70.2	23.0	Lung ca. (s.cell var.) SHP-77	14.7	21.5	15.6
Spinal cord	18.7	8.0	14.2	Lung ca. (large cell)NCI-H460	2.2	0.3	0.7
glio/astro U87-MG	2.4	3.2	1.5	Lung ca. (non-sm. cell) A549	0.0	0.0	0.0
glio/astro U-118-MG	77.4	**100.0**	**100.0**	Lung ca. (non-s.cell) NCI-H23	0.0	0.0	0.0
astrocytoma SW1783	0.0	0.6	0.3	Lung ca. (non-s.cell) HOP-62	1.3	0.9	1.4
neuro*; met SK-N-AS	1.3	9.8	2.2	Lung ca. (non-s.cl) NCI-H522	0.0	0.0	0.0
astrocytoma SF-539	0.0	0.0	0.0	Lung ca. (squam.) SW 900	5.0	4.1	5.1
astrocytoma SNB-75	5.4	3.8	6.2	Lung ca. (squam.) NCI-H596	9.9	7.1	13.7
glioma SNB-19	3.3	4.6	3.9	Mammary gland	20.2	10.1	6.9
glioma U251	15.8	3.3	10.6	Breast ca.* (pl.ef) MCF-7	0.0	0.0	0.1
glioma SF-295	10.2	10.7	14.3	Breast ca.* (pl.ef) MDA-MB-231	0.0	0.3	0.3
Heart (Fetal)	4.4	10.8	2.5	Breast ca.* (pl. ef) T47D	0.0	0.0	0.0
Heart	4.1	1.3	5.1	Breast ca. BT-549	0.0	0.0	0.0
Skeletal muscle (Fetal)	4.1	35.8	1.3	Breast ca. MDA-N	0.6	2.3	0.3

Skeletal muscle	34.2	4.5	28.3	Ovary	9.8	20.6	3.8
Bone marrow	1.3	1.7	0.3	Ovarian ca. OVCAR-3	5.6	3.3	6.3
Thymus	1.3	0.7	1.7	Ovarian ca. OVCAR-4	0.0	0.0	0.0
Spleen	1.2	1.1	2.5	Ovarian ca. OVCAR-5	0.3	0.0	0.0
Lymph node	3.9	1.8	3.0	Ovarian ca. OVCAR-8	0.8	1.8	0.7
Colorectal	15.2	10.4	6.3	Ovarian ca. IGROV-1	0.0	0.0	0.0
Stomach	6.0	2.3	4.3	Ovarian ca. (ascites) SK-OV-3	0.0	0.0	0.0
Small intestine	19.3	10.6	10.7	Uterus	3.3	0.9	3.7
Colon ca. SW480	0.0	0.0	0.0	Placenta	17.8	14.8	8.1
Colon ca.* SW620 (SW480 met)	0.2	0.0	0.0	Prostate	3.7	0.6	1.4
Colon ca. HT29	0.0	0.0	0.0	Prostate ca.* (bone met) PC-3	1.4	2.2	4.8
Colon ca. HCT-116	0.5	0.0	0.0	Testis	1.8	0.8	1.3
Colon ca. CaCo-2	0.5	0.6	0.0	Melanoma Hs688(A).T	0.0	0.0	0.1
CC Well to Mod Diff (ODO3866)	0.2	1.9	2.1	Melanoma* (met) Hs688(B).T	0.0	0.5	0.6
Colon ca. HCC-2998	0.0	0.0	0.0	Melanoma UACC-62	5.7	0.9	2.3
Gastric ca. (liver met) NCI-N87	0.0	0.0	0.0	Melanoma M14	6.1	1.3	9.2
Bladder	3.4	1.7	3.4	Melanoma LOX IMVI	0.0	0.0	0.0
Trachea	1.5	2.4	1.4	Melanoma* (met) SK-MEL-5	2.0	2.3	1.3
Kidney	13.0	4.2	20.6	Adipose	8.3	5.7	9.8

Table 14. Panel 2.2

Tissue Name	Rel. Exp.(%) Ag1492, Run 173816674	Rel. Exp.(%) Ag2441, Run 174477149	Tissue Name	Rel. Exp.(%) Ag1492, Run 173816674	Rel. Exp.(%) Ag2441, Run 174477149
Normal Colon	18.7	22.1	Kidney Margin	**100.0**	**100.0**

			(OD04348)		
Colon cancer (OD06064)	4.5	4.5	Kidney malignant cancer (OD06204B)	0.0	0.0
Colon Margin (OD06064)	46.7	34.9	Kidney normal adjacent tissue (OD06204E)	10.2	9.9
Colon cancer (OD06159)	2.2	4.1	Kidney Cancer (OD04450-01)	37.9	18.9
Colon Margin (OD06159)	30.8	36.9	Kidney Margin (OD04450-03)	28.9	39.8
Colon cancer (OD06297-04)	1.8	3.9	Kidney Cancer 8120613	0.6	1.2
Colon Margin (OD06297-015)	39.0	52.5	Kidney Margin 8120614	7.6	8.7
CC Gr.2 ascend colon (ODO3921)	4.0	2.0	Kidney Cancer 9010320	1.7	1.4
CC Margin (ODO3921)	4.6	11.2	Kidney Margin 9010321	4.4	6.3
Colon cancer metastasis (OD06104)	1.7	0.5	Kidney Cancer 8120607	0.9	0.0
Lung Margin (OD06104)	33.4	34.9	Kidney Margin 8120608	2.1	3.8
Colon mets to lung (OD04451-01)	1.9	3.0	Normal Uterus	9.9	6.6
Lung Margin (OD04451-02)	21.0	7.4	Uterine Cancer 064011	2.0	2.4
Normal Prostate	3.6	1.9	Normal Thyroid	1.7	1.1
Prostate Cancer (OD04410)	1.5	0.0	Thyroid Cancer	1.5	1.3
Prostate Margin (OD04410)	4.5	5.1	Thyroid Cancer A302152	2.1	0.3
Normal Ovary	4.2	8.5	Thyroid Margin A302153	4.0	1.8
Ovarian cancer (OD06283-03)	4.6	0.3	Normal Breast	18.9	15.8
Ovarian Margin (OD06283-07)	10.2	5.6	Breast Cancer	0.0	0.5
Ovarian Cancer	4.4	3.1	Breast Cancer	4.9	4.4
Ovarian cancer (OD06145)	4.5	5.0	Breast Cancer (OD04590-01)	2.0	2.4
Ovarian Margin	9.3	12.6	Breast Cancer	4.0	4.1

(OD06145)			Mets (OD04590-03)		
Ovarian cancer (OD06455-03)	1.5	1.6	Breast Cancer Metastasis	4.3	9.2
Ovarian Margin (OD06455-07)	9.7	4.4	Breast Cancer	3.6	1.4
Normal Lung	7.0	5.6	Breast Cancer 9100266	2.1	1.5
Invasive poor diff. lung adeno (ODO4945-01	0.6	0.0	Breast Margin 9100265	17.2	4.7
Lung Margin (ODO4945-03)	11.2	9.2	Breast Cancer A209073	3.5	2.4
Lung Malignant Cancer (OD03126)	2.8	0.5	Breast Margin A2090734	17.1	19.8
Lung Margin (OD03126)	2.0	3.8	Breast cancer (OD06083)	8.4	8.6
Lung Cancer (OD05014A)	2.0	3.6	Breast cancer node metastasis (OD06083)	2.5	3.1
Lung Margin (OD05014B)	11.3	8.4	Normal Liver	9.7	5.8
Lung cancer (OD06081)	0.3	0.8	Liver Cancer 1026	0.6	0.0
Lung Margin (OD06081)	13.2	10.5	Liver Cancer 1025	4.3	6.8
Lung Cancer (OD04237-01)	0.0	0.5	Liver Cancer 6004-T	3.3	4.9
Lung Margin (OD04237-02)	15.9	9.2	Liver Tissue 6004-N	0.8	0.6
Ocular Mel Met to Liver (ODO4310)	5.3	2.3	Liver Cancer 6005-T	1.1	0.6
Liver Margin (ODO4310)	2.2	4.0	Liver Tissue 6005-N	12.5	4.2
Melanoma Metastasis	0.0	0.2	Liver Cancer	1.0	0.6
Lung Margin (OD04321)	8.0	8.4	Normal Bladder	2.1	3.3
Normal Kidney	23.2	25.2	Bladder Cancer	0.8	0.0
Kidney Ca, Nuclear grade 2 (OD04338)	55.1	65.5	Bladder Cancer	2.2	2.6
Kidney Margin (OD04338)	2.5	2.6	Normal Stomach	15.4	9.6

Kidney Ca Nuclear grade 1/2 (OD04339)	2.2	0.8	Gastric Cancer 9060397	0.3	0.3
Kidney Margin (OD04339)	18.0	14.0	Stomach Margin 9060396	1.9	2.4
Kidney Ca, Clear cell type (OD04340)	0.8	1.2	Gastric Cancer 9060395	2.9	2.1
Kidney Margin (OD04340)	42.0	36.6	Stomach Margin 9060394	7.7	9.7
Kidney Ca, Nuclear grade 3 (OD04348)	0.3	0.7	Gastric Cancer 064005	2.7	3.6

Table 14BF. Panel 2D

Tissue Name	Rel. Exp.(%) Ag2441, Run 159616246	Tissue Name	Rel. Exp.(%) Ag2441, Run 159616246
Normal Colon	48.6	Kidney Margin 8120608	2.6
CC Well to Mod Diff (ODO3866)	0.6	Kidney Cancer 8120613	0.4
CC Margin (ODO3866)	6.6	Kidney Margin 8120614	11.5
CC Gr.2 rectosigmoid (ODO3868)	0.9	Kidney Cancer 9010320	1.7
CC Margin (ODO3868)	1.2	Kidney Margin 9010321	11.3
CC Mod Diff (ODO3920)	0.5	Normal Uterus	0.9
CC Margin (ODO3920)	9.1	Uterine Cancer 064011	3.4
CC Gr.2 ascend colon (ODO3921)	10.9	Normal Thyroid	3.9
CC Margin (ODO3921)	6.7	Thyroid Cancer	2.0
CC from Partial Hepatectomy (ODO4309) Mets	2.0	Thyroid Cancer A302152	0.6
Liver Margin (ODO4309)	3.5	Thyroid Margin A302153	10.8
Colon mets to lung (OD04451-01)	0.6	Normal Breast	12.2
Lung Margin (OD04451-02)	3.5	Breast Cancer	0.4
Normal Prostate 6546-1	1.4	Breast Cancer (OD04590-01)	7.3

Prostate Cancer (OD04410)	2.9	Breast Cancer Mets (OD04590-03)	4.8
Prostate Margin (OD04410)	8.0	Breast Cancer Metastasis	3.6
Prostate Cancer (OD04720-01)	6.6	Breast Cancer	2.0
Prostate Margin (OD04720-02)	13.3	Breast Cancer	5.4
Normal Lung	14.4	Breast Cancer 9100266	2.1
Lung Met to Muscle (ODO4286)	0.1	Breast Margin 9100265	7.4
Muscle Margin (ODO4286)	4.5	Breast Cancer A209073	8.5
Lung Malignant Cancer (OD03126)	4.3	Breast Margin A2090734	13.8
Lung Margin (OD03126)	15.0	Normal Liver	2.7
Lung Cancer (OD04404)	8.4	Liver Cancer	0.1
Lung Margin (OD04404)	3.7	Liver Cancer 1025	2.3
Lung Cancer (OD04565)	1.1	Liver Cancer 1026	0.7
Lung Margin (OD04565)	4.7	Liver Cancer 6004-T	4.0
Lung Cancer (OD04237-01)	1.2	Liver Tissue 6004-N	0.3
Lung Margin (OD04237-02)	5.6	Liver Cancer 6005-T	0.5
Ocular Mel Met to Liver (ODO4310)	2.7	Liver Tissue 6005-N	0.6
Liver Margin (ODO4310)	3.0	Normal Bladder	4.7
Melanoma Metastasis	0.7	Bladder Cancer	0.1
Lung Margin (OD04321)	8.0	Bladder Cancer	4.9
Normal Kidney	**100.0**	Bladder Cancer (OD04718-01)	0.0
Kidney Ca, Nuclear grade 2 (OD04338)	3.6	Bladder Normal Adjacent (OD04718-03)	2.8
Kidney Margin (OD04338)	32.5	Normal Ovary	7.2
Kidney Ca Nuclear grade 1/2 (OD04339)	0.5	Ovarian Cancer	6.8
Kidney Margin (OD04339)	26.8	Ovarian Cancer (OD04768-07)	0.2
Kidney Ca, Clear cell type (OD04340)	3.8	Ovary Margin (OD04768-08)	1.0
Kidney Margin (OD04340)	35.4	Normal Stomach	6.3

Kidney Ca, Nuclear grade 3 (OD04348)	0.2	Gastric Cancer 9060358	1.6
Kidney Margin (OD04348)	15.7	Stomach Margin 9060359	2.1
Kidney Cancer (OD04622-01)	1.1	Gastric Cancer 9060395	4.2
Kidney Margin (OD04622-03)	4.2	Stomach Margin 9060394	4.2
Kidney Cancer (OD04450-01)	8.0	Gastric Cancer 9060397	1.6
Kidney Margin (OD04450-03)	25.0	Stomach Margin 9060396	0.5
Kidney Cancer 8120607	0.6	Gastric Cancer 064005	8.9

Table 14BG. Panel 4D

Tissue Name	Rel. Exp.(%) Ag1492, Run 162778150	Rel. Exp.(%) Ag2441, Run 159616279	Tissue Name	Rel. Exp.(%) Ag1492, Run 162778150	Rel. Exp.(%) Ag2441, Run 159616279
Secondary Th1 act	0.0	0.0	HUVEC IL-1beta	12.5	9.6
Secondary Th2 act	0.0	0.0	HUVEC IFN gamma	5.5	6.2
Secondary Tr1 act	0.0	0.0	HUVEC TNF alpha + IFN gamma	3.6	1.9
Secondary Th1 rest	0.0	0.0	HUVEC TNF alpha + IL4	5.6	5.0
Secondary Th2 rest	0.0	0.0	HUVEC IL-11	8.5	6.5
Secondary Tr1 rest	0.0	0.0	Lung Microvascular EC none	0.4	0.1
Primary Th1 act	0.0	0.0	Lung Microvascular EC TNFalpha + IL-1beta	0.0	0.0
Primary Th2 act	0.0	0.0	Microvascular Dermal EC none	0.1	0.1
Primary Tr1 act	0.0	0.0	Microsvasular Dermal EC TNFalpha + IL-1beta	0.0	0.0
Primary Th1 rest	0.0	0.0	Bronchial epithelium TNFalpha + IL1beta	2.1	2.7

Primary Th2 rest	0.0	0.0	Small airway epithelium none	0.5	0.5
Primary Tr1 rest	0.0	0.0	Small airway epithelium TNFalpha + IL-1beta	1.1	0.8
CD45RA CD4 lymphocyte act	0.4	0.6	Coronery artery SMC rest	1.2	1.5
CD45RO CD4 lymphocyte act	0.0	0.0	Coronery artery SMC TNFalpha + IL-1beta	0.4	0.3
CD8 lymphocyte act	0.0	0.0	Astrocytes rest	1.5	1.3
Secondary CD8 lymphocyte rest	0.0	0.0	Astrocytes TNFalpha + IL-1beta	0.0	0.1
Secondary CD8 lymphocyte act	0.0	0.0	KU-812 (Basophil) rest	0.0	0.0
CD4 lymphocyte none	0.0	0.0	KU-812 (Basophil) PMA/ionomycin	0.0	0.0
2ry Th1/Th2/Tr1_anti-CD95 CH11	0.0	0.0	CCD1106 (Keratinocytes) none	0.9	0.5
LAK cells rest	0.0	0.0	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	0.0	0.1
LAK cells IL-2	0.0	0.0	Liver cirrhosis	5.7	2.6
LAK cells IL-2+IL-12	0.0	0.0	Lupus kidney	4.5	2.4
LAK cells IL-2+IFN gamma	0.0	0.0	NCI-H292 none	5.3	4.9
LAK cells IL-2+ IL-18	0.0	0.0	NCI-H292 IL-4	3.0	4.9
LAK cells PMA/ionomycin	0.0	0.0	NCI-H292 IL-9	5.2	5.3
NK Cells IL-2 rest	0.0	0.0	NCI-H292 IL-13	2.5	1.6
Two Way MLR 3 day	0.0	0.0	NCI-H292 IFN gamma	1.8	0.0
Two Way MLR 5 day	0.0	0.0	HPAEC none	3.7	5.2
Two Way MLR 7 day	0.0	0.0	HPAEC TNF alpha + IL-1 beta	6.5	4.3
PBMC rest	0.0	0.0	Lung fibroblast none	16.2	10.4
PBMC PWM	0.2	0.0	Lung fibroblast	81.2	65.5

			TNF alpha + IL-1 beta		
PBMC PHA-L	0.0	0.0	Lung fibroblast IL-4	12.0	12.9
Ramos (B cell) none	0.0	0.0	Lung fibroblast IL-9	22.2	13.3
Ramos (B cell) ionomycin	0.0	0.0	Lung fibroblast IL-13	7.9	5.9
B lymphocytes PWM	0.3	0.0	Lung fibroblast IFN gamma	10.2	7.8
B lymphocytes CD40L and IL-4	0.4	0.3	Dermal fibroblast CCD1070 rest	3.3	2.4
EOL-1 dbcAMP	0.0	0.0	Dermal fibroblast CCD1070 TNF alpha	2.5	4.5
EOL-1 dbcAMP PMA/ionomycin	0.0	0.0	Dermal fibroblast CCD1070 IL-1 beta	6.0	5.1
Dendritic cells none	0.0	0.0	Dermal fibroblast IFN gamma	2.1	0.7
Dendritic cells LPS	0.1	0.0	Dermal fibroblast IL-4	9.7	7.7
Dendritic cells anti-CD40	0.0	0.1	IBD Colitis 2	1.7	0.2
Monocytes rest	0.0	0.0	IBD Crohn's	13.7	7.7
Monocytes LPS	0.0	0.0	Colon	98.6	95.3
Macrophages rest	0.0	0.3	Lung	17.2	16.0
Macrophages LPS	0.0	0.0	Thymus	**100.0**	**100.0**
HUVEC none	11.6	5.8	Kidney	6.3	4.2
HUVEC starved	19.3	18.0			

Table 14BH. Panel CNS_1

Tissue Name	Rel. Exp.(%) Ag1492, Run 171634550	Tissue Name	Rel. Exp.(%) Ag1492, Run 171634550
BA4 Control	31.2	BA17 PSP	30.8
BA4 Control2	26.8	BA17 PSP2	31.9
BA4 Alzheimer's2	6.8	Sub Nigra Control	61.6
BA4 Parkinson's	47.3	Sub Nigra Control2	27.0
BA4 Parkinson's2	54.7	Sub Nigra Alzheimer's2	15.9
BA4 Huntington's	23.0	Sub Nigra Parkinson's2	48.3
BA4 Huntington's2	15.2	Sub Nigra Huntington's	72.2
BA4 PSP	12.3	Sub Nigra	35.1

		Huntington's2	
BA4 PSP2	37.4	Sub Nigra PSP2	17.4
BA4 Depression	20.9	Sub Nigra Depression	8.9
BA4 Depression2	17.3	Sub Nigra Depression2	12.7
BA7 Control	56.3	Glob Palladus Control	18.3
BA7 Control2	25.2	Glob Palladus Control2	11.6
BA7 Alzheimer's2	10.3	Glob Palladus Alzheimer's	22.7
BA7 Parkinson's	17.7	Glob Palladus Alzheimer's2	9.2
BA7 Parkinson's2	25.5	Glob Palladus Parkinson's	81.2
BA7 Huntington's	39.5	Glob Palladus Parkinson's2	14.7
BA7 Huntington's2	46.7	Glob Palladus PSP	3.6
BA7 PSP	42.9	Glob Palladus PSP2	12.2
BA7 PSP2	42.6	Glob Palladus Depression	14.5
BA7 Depression	16.0	Temp Pole Control	9.5
BA9 Control	45.4	Temp Pole Control2	21.9
BA9 Control2	49.3	Temp Pole Alzheimer's	14.2
BA9 Alzheimer's	2.0	Temp Pole Alzheimer's2	4.8
BA9 Alzheimer's2	19.9	Temp Pole Parkinson's	25.7
BA9 Parkinson's	37.6	Temp Pole Parkinson's2	24.5
BA9 Parkinson's2	40.1	Temp Pole Huntington's	17.3
BA9 Huntington's	46.0	Temp Pole PSP	7.2
BA9 Huntington's2	11.9	Temp Pole PSP2	2.8
BA9 PSP	21.8	Temp Pole Depression2	8.6
BA9 PSP2	4.3	Cing Gyr Control	41.2
BA9 Depression	8.5	Cing Gyr Control2	24.1
BA9 Depression2	14.7	Cing Gyr Alzheimer's	12.9

BA17 Control	**100.0**	Cing Gyr Alzheimer's2	8.4
BA17 Control2	37.1	Cing Gyr Parkinson's	25.0
BA17 Alzheimer's2	15.3	Cing Gyr Parkinson's2	23.5
BA17 Parkinson's	40.3	Cing Gyr Huntington's	54.7
BA17 Parkinson's2	62.0	Cing Gyr Huntington's2	31.4
BA17 Huntington's	33.2	Cing Gyr PSP	25.7
BA17 Huntington's2	25.7	Cing Gyr PSP2	4.6
BA17 Depression	18.6	Cing Gyr Depression	12.4
BA17 Depression2	56.3	Cing Gyr Depression2	27.7

CNS_neurodegeneration_v1.0 Summary: Ag1492/ Ag2441 Panel CNS_Neurodegeneration does not detect any difference in the expression of this gene between the postmortem brains of controls or Alzheimer's disease patients. This panel does, however, confirm the expression of this gene at moderate to high levels in the brains of an independent group of patients. See panel 1.3d for discussion of utility in the central nervous system.

Panel 1.3D Summary: Ag1492/Ag2441 The expression of this gene was assessed across 3 independent runs of panel 1.3D utilizing 2 different probe/primer sets. The runs had excellect concordance. This gene encodes a semaphorin homolog that shows an expression profile that is brain-preferential. Highest expression is seen in the brain and a cell line derived from brain cancer (CTs=28-29). Semaphorins can act as axon guidance proteins, specifically as chemorepellents that inhibit CNS regenerative capacity. Manipulation of levels of this protein may be of use in inducing a compensatory synaptogenic response to neuronal death in Alzheimer's disease, Parkinson's disease, Huntington's disease, spinocerebellar ataxia, progressive supranuclear palsy, multiple sclerosis, ALS, head trauma, stroke, or any other disease/condition associated with neuronal loss. Moreover, therapeutic modulation of this gene, through the use of small molecule drugs, antibodies or protein therapeutics might be of use in the treatment of brain cancer.

This gene is also moderately expressed in a wide variety of metabolic tissues, including pancreas, adrenal, thyroid, pituitary, adult and fetal heart, adult and fetal skeletal muscle, adult and fetal liver, and adipose. This suggests that this gene product may be important for the pathogenesis, diagnosis, and/or treatment of metabolic diseases including obesity and Types 1 and 2 diabetes.

Panel 2.2 Summary: Ag1492/2441

The expression of this gene was assessed in two independent runs in panel 2.2 using different probe/primer pairs with good concordance. This gene was found to show highest expression in a sample derived from normal kidney adjacent to a kidney cancer. This pattern of expression was consistent for other normal kidney/kidney cancer pairs as well as for normal colon/colon cancer pairs. Thus, the expression of this gene could be used to distinguish normal colon and kidney tissue from the other samples in the panel, and in particular, their genetically related malignant counterparts. Morover, therapeutic modulation of this gene, through the use of small

molecule drugs, antibodies or protein therapeutics might be of use in the treatment of kidney or colon cancer.

Panel 2D Summary: Ag2441 This gene is most highly expressed in a sample derived from normal kidney tissue. This pattern of expression is consistent for other normal kidney/kidney cancer pairs as well as being consistent with Panel 2.2. Thus, the expression of this gene could be used to distinguish normal kidney tissue from the other samples in the panel, and in particular, their genetically related malignant counterparts. Moreover, therapeutic modulation of this gene, through the use of small molecule drugs, antibodies or protein therapeutics might be of use in the treatment of kidney cancer.

Panel 4D Summary: Ag1492/2441 This gene encodes a semaphoring homolog and is expressed at a high level (CTs=28) in TNF-alpha + IL-1-beta-stimulated lung epithelial cells, colon, and thymus. Thus, this gene product be a useful protein therapeutic to reduce or eliminate the symptoms of chronic obstructive pulmonary disease, asthma, emphysema, and ulcerative colitis.

Panel CNS_1 Summary: Ag1492 This panel confirms the expression of this semaphorin precursor in the adult central nervous system. See panel 1.3d for a discussion of utility in the central nervous system.

C. NOV5 (CG50211-01 and CG50211-02: serine/threonine kinase)

Expression of gene CG50211-01 and variant CG50211-02 was assessed using the primer-probe set Ag2492, described in Table 15CA. Results of the RTQ-PCR runs are shown in Tables 15CB, 15CC, 15CD and 15CE.

Table 15CA. Probe Name Ag2492

Primers	Sequences	Length	Start Position
Forward	5'-cagaagctgttccgagaagtc-3' (SEQ ID NO: 131)	21	501
Probe	TET-5'-atgaagggcctaaaccaccccaacat-3'-TAMRA (SEQ ID NO: 132)	26	528
Reverse	5'-caatcacctcaaagagcttcac-3' (SEQ ID NO: 133)	22	555

Table 15CB. CNS_neurodegeneration_v1.0

Tissue Name	Rel. Exp.(%) Ag2492, Run 208778160	Tissue Name	Rel. Exp.(%) Ag2492, Run 208778160
AD 1 Hippo	18.4	Control (Path) 3 Temporal Ctx	6.0
AD 2 Hippo	33.4	Control (Path) 4 Temporal Ctx	27.0
AD 3 Hippo	10.4	AD 1 Occipital Ctx	14.6
AD 4 Hippo	9.4	AD 2 Occipital Ctx (Missing)	0.0
AD 5 Hippo	96.6	AD 3 Occipital Ctx	6.6
AD 6 Hippo	85.3	AD 4 Occipital Ctx	19.5
Control 2 Hippo	52.5	AD 5 Occipital Ctx	37.1
Control 4 Hippo	9.9	AD 5 Occipital Ctx	87.1
Control (Path) 3 Hippo	5.4	Control 1 Occipital Ctx	3.5
AD 1 Temporal Ctx	18.8	Control 2 Occipital	85.3

		Ctx	
AD 2 Temporal Ctx	34.9	Control 3 Occipital Ctx	13.7
AD 3 Temporal Ctx	8.2	Control 4 Occipital Ctx	7.2
AD 4 Temporal Ctx	18.9	Control (Path) 1 Occipital Ctx	82.9
AD 5 Inf Temporal Ctx	94.0	Control (Path) 2 Occipital Ctx	6.7
AD 5 Sup Temporal Ctx	52.9	Control (Path) 3 Occipital Ctx	4.0
AD 6 Inf Temporal Ctx	69.3	Control (Path) 4 Occipital Ctx	11.6
AD 6 Sup Temporal Ctx	64.6	Control 1 Parietal Ctx	4.7
Control 1 Temporal Ctx	6.3	Control 2 Parietal Ctx	47.0
Control 2 Temporal Ctx	69.3	Control 3 Parietal Ctx	18.4
Control 3 Temporal Ctx	14.9	Control (Path) 1 Parietal Ctx	**100.0**
Control 3 Temporal Ctx	13.2	Control (Path) 2 Parietal Ctx	21.2
Control (Path) 1 Temporal Ctx	82.4	Control (Path) 3 Parietal Ctx	5.5
Control (Path) 2 Temporal Ctx	34.6	Control (Path) 4 Parietal Ctx	36.9

Table 15CC. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2492, Run 159841006	Tissue Name	Rel. Exp.(%) Ag2492, Run 159841006
Liver adenocarcinoma	22.7	Kidney (fetal)	11.0
Pancreas	2.3	Renal ca. 786-0	8.1
Pancreatic ca. CAPAN 2	2.2	Renal ca. A498	23.8
Adrenal gland	5.0	Renal ca. RXF 393	3.7
Thyroid	5.7	Renal ca. ACHN	4.1
Salivary gland	3.9	Renal ca. UO-31	9.7
Pituitary gland	8.7	Renal ca. TK-10	3.9
Brain (fetal)	22.8	Liver	3.4
Brain (whole)	18.7	Liver (fetal)	7.7
Brain (amygdala)	24.1	Liver ca. (hepatoblast) HepG2	13.4
Brain (cerebellum)	7.9	Lung	12.7
Brain (hippocampus)	88.9	Lung (fetal)	8.4

Brain (substantia nigra)	4.7	Lung ca. (small cell) LX-1	4.2
Brain (thalamus)	26.1	Lung ca. (small cell) NCI-H69	14.1
Cerebral Cortex	**100.0**	Lung ca. (s.cell var.) SHP-77	12.8
Spinal cord	6.6	Lung ca. (large cell)NCI-H460	16.5
glio/astro U87-MG	9.5	Lung ca. (non-sm. cell) A549	4.4
glio/astro U-118-MG	17.4	Lung ca. (non-s.cell) NCI-H23	21.2
astrocytoma SW1783	14.1	Lung ca. (non-s.cell) HOP-62	26.2
neuro*; met SK-N-AS	54.0	Lung ca. (non-s.cl) NCI-H522	5.5
astrocytoma SF-539	15.5	Lung ca. (squam.) SW 900	6.7
astrocytoma SNB-75	16.8	Lung ca. (squam.) NCI-H596	2.9
glioma SNB-19	14.9	Mammary gland	15.0
glioma U251	6.7	Breast ca.* (pl.ef) MCF-7	8.2
glioma SF-295	11.9	Breast ca.* (pl.ef) MDA-MB-231	25.9
Heart (Fetal)	42.0	Breast ca.* (pl. ef) T47D	3.7
Heart	3.3	Breast ca. BT-549	26.6
Skeletal muscle (Fetal)	54.7	Breast ca. MDA-N	7.6
Skeletal muscle	3.4	Ovary	40.6
Bone marrow	2.2	Ovarian ca. OVCAR-3	6.6
Thymus	5.9	Ovarian ca. OVCAR-4	4.2
Spleen	8.0	Ovarian ca. OVCAR-5	6.7
Lymph node	3.3	Ovarian ca. OVCAR-8	8.5
Colorectal	8.0	Ovarian ca. IGROV-1	3.4
Stomach	6.2	Ovarian ca. (ascites) SK-OV-3	12.2
Small intestine	5.3	Uterus	5.5
Colon ca. SW480	5.5	Placenta	4.9
Colon ca.* SW620	2.5	Prostate	3.9

(SW480 met)			
Colon ca. HT29	6.0	Prostate ca.* (bone met) PC-3	4.5
Colon ca. HCT-116	6.6	Testis	31.4
Colon ca. CaCo-2	9.9	Melanoma Hs688(A).T	2.6
CC Well to Mod Diff (ODO3866)	7.9	Melanoma* (met) Hs688(B).T	3.9
Colon ca. HCC-2998	25.9	Melanoma UACC-62	2.7
Gastric ca. (liver met) NCI-N87	22.4	Melanoma M14	4.3
Bladder	4.6	Melanoma LOX IMVI	9.9
Trachea	10.0	Melanoma* (met) SK-MEL-5	5.9
Kidney	2.5	Adipose	4.5

Table 15CD. Panel 2D

Tissue Name	Rel. Exp.(%) Ag2492, Run 159841210	Tissue Name	Rel. Exp.(%) Ag2492, Run 159841210
Normal Colon	46.7	Kidney Margin 8120608	17.4
CC Well to Mod Diff (ODO3866)	9.7	Kidney Cancer 8120613	36.1
CC Margin (ODO3866)	11.6	Kidney Margin 8120614	29.5
CC Gr.2 rectosigmoid (ODO3868)	11.6	Kidney Cancer 9010320	31.2
CC Margin (ODO3868)	5.1	Kidney Margin 9010321	31.0
CC Mod Diff (ODO3920)	21.2	Normal Uterus	9.0
CC Margin (ODO3920)	20.4	Uterine Cancer 064011	29.1
CC Gr.2 ascend colon (ODO3921)	27.7	Normal Thyroid	17.4
CC Margin (ODO3921)	8.9	Thyroid Cancer	23.8
CC from Partial Hepatectomy (ODO4309) Mets	17.9	Thyroid Cancer A302152	15.7
Liver Margin (ODO4309)	19.1	Thyroid Margin A302153	18.3
Colon mets to lung (OD04451-01)	16.6	Normal Breast	27.0
Lung Margin (OD04451-02)	13.1	Breast Cancer	53.2

Normal Prostate 6546-1	12.2	Breast Cancer (OD04590-01)	**100.0**
Prostate Cancer (OD04410)	35.1	Breast Cancer Mets (OD04590-03)	66.4
Prostate Margin (OD04410)	37.4	Breast Cancer Metastasis	92.0
Prostate Cancer (OD04720-01)	33.2	Breast Cancer	20.7
Prostate Margin (OD04720-02)	41.8	Breast Cancer	41.5
Normal Lung	35.4	Breast Cancer 9100266	38.2
Lung Met to Muscle (ODO4286)	17.2	Breast Margin 9100265	24.0
Muscle Margin (ODO4286)	22.8	Breast Cancer A209073	44.8
Lung Malignant Cancer (OD03126)	17.2	Breast Margin A2090734	25.9
Lung Margin (OD03126)	33.4	Normal Liver	11.1
Lung Cancer (OD04404)	41.5	Liver Cancer	15.3
Lung Margin (OD04404)	17.2	Liver Cancer 1025	13.6
Lung Cancer (OD04565)	25.5	Liver Cancer 1026	16.6
Lung Margin (OD04565)	13.9	Liver Cancer 6004-T	15.4
Lung Cancer (OD04237-01)	31.2	Liver Tissue 6004-N	11.4
Lung Margin (OD04237-02)	23.0	Liver Cancer 6005-T	17.9
Ocular Mel Met to Liver (ODO4310)	35.1	Liver Tissue 6005-N	7.6
Liver Margin (ODO4310)	14.7	Normal Bladder	36.6
Melanoma Metastasis	21.3	Bladder Cancer	12.9
Lung Margin (OD04321)	28.3	Bladder Cancer	19.1
Normal Kidney	46.3	Bladder Cancer (OD04718-01)	34.6
Kidney Ca, Nuclear grade 2 (OD04338)	37.4	Bladder Normal Adjacent (OD04718-03)	34.2
Kidney Margin (OD04338)	32.3	Normal Ovary	31.4
Kidney Ca Nuclear grade 1/2 (OD04339)	20.6	Ovarian Cancer	36.1
Kidney Margin (OD04339)	32.1	Ovarian Cancer (OD04768-07)	30.1
Kidney Ca, Clear cell type (OD04340)	52.5	Ovary Margin (OD04768-08)	12.9

Kidney Margin (OD04340)	40.9	Normal Stomach	22.2
Kidney Ca, Nuclear grade 3 (OD04348)	15.9	Gastric Cancer 9060358	8.5
Kidney Margin (OD04348)	20.9	Stomach Margin 9060359	20.2
Kidney Cancer (OD04622-01)	23.5	Gastric Cancer 9060395	27.0
Kidney Margin (OD04622-03)	9.3	Stomach Margin 9060394	23.2
Kidney Cancer (OD04450-01)	14.8	Gastric Cancer 9060397	17.7
Kidney Margin (OD04450-03)	27.5	Stomach Margin 9060396	12.8
Kidney Cancer 8120607	19.5	Gastric Cancer 064005	31.2

Table 15CE. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2492, Run 164033742	Tissue Name	Rel. Exp.(%) Ag2492, Run 164033742
Secondary Th1 act	17.9	HUVEC IL-1beta	10.7
Secondary Th2 act	19.2	HUVEC IFN gamma	23.0
Secondary Tr1 act	23.8	HUVEC TNF alpha + IFN gamma	14.3
Secondary Th1 rest	4.9	HUVEC TNF alpha + IL4	14.1
Secondary Th2 rest	9.3	HUVEC IL-11	18.3
Secondary Tr1 rest	7.2	Lung Microvascular EC none	18.8
Primary Th1 act	18.0	Lung Microvascular EC TNFalpha + IL-1beta	19.9
Primary Th2 act	12.2	Microvascular Dermal EC none	30.4
Primary Tr1 act	22.5	Microsvasular Dermal EC TNFalpha + IL-1beta	16.8
Primary Th1 rest	27.2	Bronchial epithelium TNFalpha + IL1beta	8.7
Primary Th2 rest	23.3	Small airway epithelium none	18.3
Primary Tr1 rest	11.7	Small airway epithelium TNFalpha + IL-1beta	**100.0**
CD45RA CD4 lymphocyte act	8.8	Coronery artery SMC rest	31.9
CD45RO CD4 lymphocyte act	19.5	Coronery artery SMC TNFalpha + IL-1beta	22.7
CD8 lymphocyte act	9.3	Astrocytes rest	27.9

Secondary CD8 lymphocyte rest	12.7	Astrocytes TNFalpha + IL-1beta	21.8
Secondary CD8 lymphocyte act	9.7	KU-812 (Basophil) rest	10.4
CD4 lymphocyte none	4.7	KU-812 (Basophil) PMA/ionomycin	28.3
2ry Th1/Th2/Tr1_anti-CD95 CH11	9.0	CCD1106 (Keratinocytes) none	15.0
LAK cells rest	7.7	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	3.2
LAK cells IL-2	15.5	Liver cirrhosis	3.7
LAK cells IL-2+IL-12	11.0	Lupus kidney	3.4
LAK cells IL-2+IFN gamma	14.9	NCI-H292 none	30.6
LAK cells IL-2+ IL-18	12.0	NCI-H292 IL-4	39.8
LAK cells PMA/ionomycin	5.6	NCI-H292 IL-9	70.2
NK Cells IL-2 rest	10.2	NCI-H292 IL-13	18.4
Two Way MLR 3 day	11.7	NCI-H292 IFN gamma	27.7
Two Way MLR 5 day	6.2	HPAEC none	24.1
Two Way MLR 7 day	6.9	HPAEC TNF alpha + IL-1 beta	25.3
PBMC rest	7.2	Lung fibroblast none	15.3
PBMC PWM	29.5	Lung fibroblast TNF alpha + IL-1 beta	14.1
PBMC PHA-L	13.8	Lung fibroblast IL-4	36.9
Ramos (B cell) none	6.4	Lung fibroblast IL-9	28.9
Ramos (B cell) ionomycin	36.6	Lung fibroblast IL-13	22.4
B lymphocytes PWM	48.0	Lung fibroblast IFN gamma	53.6
B lymphocytes CD40L and IL-4	20.2	Dermal fibroblast CCD1070 rest	40.1
EOL-1 dbcAMP	15.8	Dermal fibroblast CCD1070 TNF alpha	74.7
EOL-1 dbcAMP PMA/ionomycin	31.9	Dermal fibroblast CCD1070 IL-1 beta	19.5
Dendritic cells none	10.9	Dermal fibroblast IFN gamma	11.5
Dendritic cells LPS	10.0	Dermal fibroblast IL-4	31.0
Dendritic cells anti-CD40	6.8	IBD Colitis 2	0.9
Monocytes rest	9.9	IBD Crohn's	1.9
Monocytes LPS	13.5	Colon	14.6
Macrophages rest	11.1	Lung	21.2

Macrophages LPS	7.6	Thymus	25.2
HUVEC none	26.2	Kidney	49.3
HUVEC starved	40.6		

CNS_neurodegeneration_v1.0 Summary: Ag2492 Panel CNS_Neurodegeneration does not detect any difference in the expression of this gene between the postmortem brains of controls or Alzheimer's disease patients. This panel does, however, confirm the expression of this gene at moderate levels in the brains of an independent group of patients. See panel 1.3d for discussion of utility in the central nervous system.

Panel 1.3D Summary: Ag2492 This gene encodes a serine/threonine kinase homolog that is expressed in moderate to high levels in the CNS, with highest expression in the cerebral cortex (CT=26.5). Serine/threonine kinases are activated by antidepressants; this gene may therefore be a small molecule target for the treatment of depression or bipolar disorder.

This gene is moderately expressed in a number of metabolic tissues including pancreas, adrenal, pituitary, thyroid, adult and fetal heart, adult and fetal skeletal muscle, adult and fetal liver, and adipose. This suggests that this kinase may be a small molecule target for the treatment of metabolic disease, including obesity and Types 1 and 2 diabetes. This gene is also expressed at higher levels in fetal heart and skeletal muscle(CTs=27.5) than in adult heart and skeletal muscle (CTs=31.5). This suggests that the expression of this gene could be used to differentiate between the adult and fetal sources of this tissue. Furthermore, the higher levels of expression in the fetal tissue suggest that the protein encoded by this gene may be involved in the development of these organs. Thus, therapeutic modulation of the expression or function of the gene product may be useful in treating disease that effect the heart and skeletal muscle.

There is also consistent expression in tissues derived from brain cancer cell lines, in addition to the expression in normal brain. Thus, the expression of this gene could be used to distinguish tissues or cell lines derived from brain from other samples in the panel. Moreover, therapeutic modulation of this gene, through the use of small molecule drugs, antibodies or protein therapeutics might be of benefit in the treatment of brain cancer.

References:

Popoli M, Mori S, Brunello N, Perez J, Gennarelli M, Racagni G.Serine/threonine kinases as molecular targets of antidepressants: implications for pharmacological treatment and pathophysiology of affective disorders. Pharmacol Ther 2001 Feb;89(2):149-70

It is currently a widely accepted opinion that adaptive, plastic changes in the molecular and cellular components of neuronal signaling systems correlate with the effects on mood and cognition observed after long-term treatment with antidepressant drugs. Protein phosphorylation represents a key step for most signaling systems, and it is involved in the regulation of virtually all cellular functions. Two serine/threonine kinases, Ca2+ /calmodulin-dependent protein kinase II and cyclic AMP-dependent protein kinase, have been shown to be activated in the brain following antidepressant treatment. The changes in kinase activity are mirrored by changes in the phosphorylation of selected protein substrates in subcellular compartments (presynaptic terminals and microtubules), which, in turn, may contribute to the modulation of synaptic transmission observed with antidepressants. The molecular consequences of protein kinase activation may account for some of the alterations in neural function induced by antidepressants, and may suggest novel possible strategies of pharmacological intervention.

Panel 2D Summary: Ag2492 The expression of this gene in panel 2D appears to be highest in a sample derived from a breast cancer (CT=28.6). There is also substantial expression in other breast cancers as well. Thus, the expression of this gene could be used to distinguish breast cancer samples from other samples in the panel. Moreover, therapeutic modulation of

this gene, through the use of small molecule drugs, antibodies or protein therapeutics might be of benefit in the treatment of breast cancer.

Panel 4D Summary: Ag2492 This gene encodes a serine/threonine protein kinasehomolog and is expressed at a moderate level in all cells and tissues in this panel, with highest expression in TNF-alpha + IL-1-beta stimulated small airway epithelium, IL-9-stimulated NCI-H292 pulmonary mucoepidermoid cells, and TNF-alpha-stimulated CCD1070 dermal fibroblasts(CTs=27.5). This expression profile suggests that small molecule drugs that inhibit this novel serine/threonine protein kinase-like protein may be useful therapeutics that reduce or eliminate the symptoms of chronic obstructive pulmonary disease, asthma, emphysema, and psoriasis.

D. NOV6 (CG50215-01 and CG50215-04)

Expression of gene CG50215-01 and variant CG50215-04 was assessed using the primer-probe set Ag2493, described in Table 16DA. Results of the RTQ-PCR runs are shown in Tables 16DB, 16DC and 16DD.

Table 16DA. Probe Name Ag2493

Primers	Sequences	Length	Start Position
Forward	5'-agaacacccctggctccta-3' (SEQ ID NO: 134)	19	2865
Probe	TET-5'-acaccagcctgtgaccctggctat-3'-TAMRA (SEQ ID NO: 135)	24	2891
Reverse	5'-gtttcacactcgttcacatcct-3' (SEQ ID NO: 136)	22	2940

Table 16DB. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2493, Run 165630586	Tissue Name	Rel. Exp.(%) Ag2493, Run 165630586
Liver adenocarcinoma	0.0	Kidney (fetal)	3.9
Pancreas	0.0	Renal ca. 786-0	0.0
Pancreatic ca. CAPAN 2	36.6	Renal ca. A498	0.0
Adrenal gland	0.0	Renal ca. RXF 393	0.0
Thyroid	0.0	Renal ca. ACHN	0.0
Salivary gland	0.0	Renal ca. UO-31	0.0
Pituitary gland	0.0	Renal ca. TK-10	21.9
Brain (fetal)	5.6	Liver	0.0
Brain (whole)	0.0	Liver (fetal)	7.6
Brain (amygdala)	6.6	Liver ca. (hepatoblast) HepG2	0.0
Brain (cerebellum)	0.0	Lung	0.0
Brain (hippocampus)	0.0	Lung (fetal)	0.0
Brain (substantia nigra)	0.0	Lung ca. (small cell) LX-1	0.0
Brain (thalamus)	0.0	Lung ca. (small cell) NCI-H69	0.0
Cerebral Cortex	13.5	Lung ca. (s.cell var.) SHP-77	0.0
Spinal cord	0.0	Lung ca. (large	2.3

		cell)NCI-H460	
glio/astro U87-MG	5.3	Lung ca. (non-sm. cell) A549	13.6
glio/astro U-118-MG	7.7	Lung ca. (non-s.cell) NCI-H23	7.5
astrocytoma SW1783	5.6	Lung ca. (non-s.cell) HOP-62	0.0
neuro*; met SK-N-AS	0.0	Lung ca. (non-s.cl) NCI-H522	0.0
astrocytoma SF-539	0.0	Lung ca. (squam.) SW 900	0.0
astrocytoma SNB-75	0.0	Lung ca. (squam.) NCI-H596	0.0
glioma SNB-19	0.0	Mammary gland	0.0
glioma U251	13.3	Breast ca.* (pl.ef) MCF-7	26.4
glioma SF-295	0.0	Breast ca.* (pl.ef) MDA-MB-231	0.0
Heart (Fetal)	0.0	Breast ca.* (pl. ef) T47D	8.8
Heart	0.0	Breast ca. BT-549	0.0
Skeletal muscle (Fetal)	0.0	Breast ca. MDA-N	13.7
Skeletal muscle	0.0	Ovary	0.0
Bone marrow	0.0	Ovarian ca. OVCAR-3	27.9
Thymus	0.0	Ovarian ca. OVCAR-4	0.0
Spleen	0.0	Ovarian ca. OVCAR-5	17.7
Lymph node	11.0	Ovarian ca. OVCAR-8	0.0
Colorectal	10.2	Ovarian ca. IGROV-1	0.0
Stomach	0.0	Ovarian ca. (ascites) SK-OV-3	0.0
Small intestine	0.0	Uterus	0.0
Colon ca. SW480	0.0	Placenta	0.0
Colon ca.* SW620 (SW480 met)	0.0	Prostate	**100.0**
Colon ca. HT29	0.0	Prostate ca.* (bone met) PC-3	8.8
Colon ca. HCT-116	0.0	Testis	0.0
Colon ca. CaCo-2	22.1	Melanoma Hs688(A).T	0.0
CC Well to Mod Diff	7.0	Melanoma* (met)	0.0

(ODO3866)		Hs688(B).T	
Colon ca. HCC-2998	0.0	Melanoma UACC-62	3.9
Gastric ca. (liver met) NCI-N87	0.0	Melanoma M14	0.0
Bladder	0.0	Melanoma LOX IMVI	0.0
Trachea	0.0	Melanoma* (met) SK-MEL-5	0.0
Kidney	0.0	Adipose	28.1

Table 16DC. Panel 2.2

Tissue Name	Rel. Exp.(%) Ag2493, Run 174926557	Tissue Name	Rel. Exp.(%) Ag2493, Run 174926557
Normal Colon	10.0	Kidney Margin (OD04348)	7.2
Colon cancer (OD06064)	2.4	Kidney malignant cancer (OD06204B)	0.6
Colon Margin (OD06064)	7.2	Kidney normal adjacent tissue (OD06204E)	6.7
Colon cancer (OD06159)	2.7	Kidney Cancer (OD04450-01)	0.5
Colon Margin (OD06159)	7.2	Kidney Margin (OD04450-03)	3.0
Colon cancer (OD06297-04)	1.0	Kidney Cancer 8120613	0.4
Colon Margin (OD06297-015)	10.2	Kidney Margin 8120614	4.6
CC Gr.2 ascend colon (ODO3921)	3.7	Kidney Cancer 9010320	2.0
CC Margin (ODO3921)	0.6	Kidney Margin 9010321	1.8
Colon cancer metastasis (OD06104)	0.8	Kidney Cancer 8120607	6.9
Lung Margin (OD06104)	4.3	Kidney Margin 8120608	2.6
Colon mets to lung (OD04451-01)	4.0	Normal Uterus	16.4
Lung Margin (OD04451-02)	5.8	Uterine Cancer 064011	13.7
Normal Prostate	11.7	Normal Thyroid	6.5
Prostate Cancer (OD04410)	3.2	Thyroid Cancer	4.5
Prostate Margin (OD04410)	7.5	Thyroid Cancer A302152	8.8
Normal Ovary	**100.0**	Thyroid Margin	4.2

		A302153	
Ovarian cancer (OD06283-03)	1.6	Normal Breast	7.1
Ovarian Margin (OD06283-07)	3.5	Breast Cancer	2.2
Ovarian Cancer	2.2	Breast Cancer	6.8
Ovarian cancer (OD06145)	2.9	Breast Cancer (OD04590-01)	16.7
Ovarian Margin (OD06145)	20.9	Breast Cancer Mets (OD04590-03)	5.4
Ovarian cancer (OD06455-03)	1.9	Breast Cancer Metastasis	8.0
Ovarian Margin (OD06455-07)	9.7	Breast Cancer	0.7
Normal Lung	12.1	Breast Cancer 9100266	2.2
Invasive poor diff. lung adeno (ODO4945-01	0.8	Breast Margin 9100265	1.3
Lung Margin (ODO4945-03)	4.8	Breast Cancer A209073	1.7
Lung Malignant Cancer (OD03126)	2.3	Breast Margin A2090734	6.3
Lung Margin (OD03126)	4.1	Breast cancer (OD06083)	3.1
Lung Cancer (OD05014A)	4.1	Breast cancer node metastasis (OD06083)	1.2
Lung Margin (OD05014B)	2.8	Normal Liver	0.7
Lung cancer (OD06081)	10.2	Liver Cancer 1026	3.0
Lung Margin (OD06081)	4.7	Liver Cancer 1025	3.4
Lung Cancer (OD04237-01)	0.6	Liver Cancer 6004-T	1.6
Lung Margin (OD04237-02)	12.1	Liver Tissue 6004-N	0.6
Ocular Mel Met to Liver (ODO4310)	1.5	Liver Cancer 6005-T	8.0
Liver Margin (ODO4310)	2.9	Liver Tissue 6005-N	9.2
Melanoma Metastasis	0.5	Liver Cancer	0.3
Lung Margin (OD04321)	6.6	Normal Bladder	0.4
Normal Kidney	1.9	Bladder Cancer	0.6
Kidney Ca, Nuclear grade 2 (OD04338)	6.8	Bladder Cancer	1.5
Kidney Margin	0.0	Normal Stomach	30.4

(OD04338)			
Kidney Ca Nuclear grade 1/2 (OD04339)	1.5	Gastric Cancer 9060397	1.9
Kidney Margin (OD04339)	1.8	Stomach Margin 9060396	7.4
Kidney Ca, Clear cell type (OD04340)	2.0	Gastric Cancer 9060395	9.1
Kidney Margin (OD04340)	1.1	Stomach Margin 9060394	12.6
Kidney Ca, Nuclear grade 3 (OD04348)	0.9	Gastric Cancer 064005	3.5

Table 16DD. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2493, Run 164317906	Tissue Name	Rel. Exp.(%) Ag2493, Run 164317906
Secondary Th1 act	7.1	HUVEC IL-1beta	3.7
Secondary Th2 act	13.6	HUVEC IFN gamma	3.2
Secondary Tr1 act	12.4	HUVEC TNF alpha + IFN gamma	5.7
Secondary Th1 rest	4.1	HUVEC TNF alpha + IL4	6.5
Secondary Th2 rest	7.7	HUVEC IL-11	5.5
Secondary Tr1 rest	4.6	Lung Microvascular EC none	10.7
Primary Th1 act	14.7	Lung Microvascular EC TNFalpha + IL-1beta	3.9
Primary Th2 act	19.6	Microvascular Dermal EC none	13.6
Primary Tr1 act	25.7	Microsvasular Dermal EC TNFalpha + IL-1beta	16.3
Primary Th1 rest	22.7	Bronchial epithelium TNFalpha + IL1beta	45.7
Primary Th2 rest	17.3	Small airway epithelium none	10.8
Primary Tr1 rest	12.5	Small airway epithelium TNFalpha + IL-1beta	54.7
CD45RA CD4 lymphocyte act	7.0	Coronery artery SMC rest	63.7
CD45RO CD4 lymphocyte act	14.4	Coronery artery SMC TNFalpha + IL-1beta	22.8
CD8 lymphocyte act	10.7	Astrocytes rest	3.1
Secondary CD8 lymphocyte rest	16.5	Astrocytes TNFalpha + IL-1beta	0.8
Secondary CD8 lymphocyte act	7.4	KU-812 (Basophil) rest	16.8
CD4 lymphocyte none	10.6	KU-812 (Basophil)	46.0

		PMA/ionomycin	
2ry Th1/Th2/Tr1_anti-CD95 CH11	7.3	CCD1106 (Keratinocytes) none	28.1
LAK cells rest	7.3	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	21.3
LAK cells IL-2	7.0	Liver cirrhosis	9.5
LAK cells IL-2+IL-12	6.9	Lupus kidney	5.0
LAK cells IL-2+IFN gamma	18.4	NCI-H292 none	3.3
LAK cells IL-2+ IL-18	8.4	NCI-H292 IL-4	1.9
LAK cells PMA/ionomycin	20.0	NCI-H292 IL-9	3.2
NK Cells IL-2 rest	4.8	NCI-H292 IL-13	1.7
Two Way MLR 3 day	6.6	NCI-H292 IFN gamma	0.6
Two Way MLR 5 day	4.5	HPAEC none	3.7
Two Way MLR 7 day	6.6	HPAEC TNF alpha + IL-1 beta	4.8
PBMC rest	8.7	Lung fibroblast none	81.8
PBMC PWM	27.7	Lung fibroblast TNF alpha + IL-1 beta	20.3
PBMC PHA-L	17.7	Lung fibroblast IL-4	**100.0**
Ramos (B cell) none	5.3	Lung fibroblast IL-9	59.5
Ramos (B cell) ionomycin	27.0	Lung fibroblast IL-13	49.0
B lymphocytes PWM	46.3	Lung fibroblast IFN gamma	95.3
B lymphocytes CD40L and IL-4	15.4	Dermal fibroblast CCD1070 rest	15.7
EOL-1 dbcAMP	7.2	Dermal fibroblast CCD1070 TNF alpha	23.3
EOL-1 dbcAMP PMA/ionomycin	2.3	Dermal fibroblast CCD1070 IL-1 beta	8.8
Dendritic cells none	4.1	Dermal fibroblast IFN gamma	24.5
Dendritic cells LPS	0.0	Dermal fibroblast IL-4	0.0
Dendritic cells anti-CD40	3.3	IBD Colitis 2	0.7
Monocytes rest	3.6	IBD Crohn's	2.6
Monocytes LPS	0.8	Colon	61.6
Macrophages rest	4.9	Lung	52.5
Macrophages LPS	2.2	Thymus	25.9
HUVEC none	7.3	Kidney	28.9
HUVEC starved	15.7		

Panel 1.3D Summary: Ag2493 Expression of this gene is restricted to the prostate (CT=34.4). Thus, expression of this gene could be used to differentiate prostate tissue from other tissues.

Panel 2.2 Summary: Ag2493 The expression of this gene appears to be restricted to a sample derived from normal ovary and a sample of normal ovary adjacent to an ovarian cancer. Of note is the observed lack of expression in ovarian cancer tissues. Thus, the expression of this gene could be used to distinguish normal ovarian tissues from other tissues in the panel and specifically ovarian cancer tissue. Therefore, expression of this gene could be used in the diagnosis or prognosis of ovarian cancer. Moreover, therapeutic modulation of this gene, through the use of small molecule drugs, antibodies or protein therapeutics could benefit in the treatment of ovarian cancer.

Panel 4D Summary: Ag2493 This gene encodes a TGF-beta binding protein 4 homolog. TGF-beta binding protein 4 is a secreted protein that regulates the activity of members of the TGF-beta family of growth factors. This gene is expressed at a moderate level in TNF-alpha + IL-1-beta-activated bronchial epithelium, TNF-alpha + IL-1-beta-activated small airway epithelium, resting lung fibroblasts, and IL-4 or IL-9 or IL-13 or IFN-gamma-activated lung fibroblasts. Thus, this gene product may be a useful therapeutic protein to reduce or eliminate the symptoms of chronic obstructive pulmonary disease. Furthermore, the protein encoded by this gene may also be useful as a therapeutic to reduce or eliminate the symptoms of other diseases whose pathophysiology is controlled in part by TGF-beta family members, such as osteoarthritis and rheumatoid arthritis.

References:

Iemura S, Yamamoto TS, Takagi C, Kobayashi H, Ueno N. J Biol Chem 1999 Sep 17;274(38):26843-9 Isolation and characterization of bone morphogenetic protein-binding proteins from the early Xenopus embryo.

Using a surface plasmon resonance biosensor as a sensitive and specific monitor, we have isolated two distinct bone morphogenetic protein (BMP)-binding proteins, and identified them as lipovitellin 1 and Ep45, respectively. Lipovitellin 1 is an egg yolk protein that is processed from vitellogenin. Both vitellogenin and Ep45 are synthesized under estrogen control in the liver, secreted, and taken up by developing oocytes. In this paper, we have shown that of the TGF-beta family members tested, Ep45 can bind only to BMP-4, whereas lipovitellin 1 can bind to both BMP-4 and activin A. Because of this difference in specificity, we have focused on and further studied Ep45. Kinetic parameters were determined by surface plasmon resonance studies and showed that Ep45 associated rapidly with BMP-4 (k(a) = 1.06 x 10(4) M(-1)s(-1)) and dissociated slowly (k(d) = 1.6 x 10(-4) s(-1)). In Xenopus embryos microinjected with Ep45 mRNA, Ep45 blocked the ability of follistatin to inhibit BMP activity and to induce a secondary body axis in a dose-dependent manner, whereas it had no effect on other BMP antagonists, chordin and noggin. These results support the possibility that Ep45 interacts with BMP to modulate its activities in vivo.

Dale L, Wardle FC. Semin Cell Dev Biol 1999 Jun;10(3):319-26 A gradient of BMP activity specifies dorsal-ventral fates in early Xenopus embryos.

BMP-4 is an extracellular signalling molecule belonging to the TGF-beta superfamily that plays a central role in dorsoventral patterning in vertebrate gastrulae. We review the evidence indicating that BMP-4 acts as a morphogen, specifying dorsoventral positional values in a concentration-dependent manner. An activity gradient of BMP-4 is established not by simple diffusion from a localised source, but by diffusion of inhibitory binding proteins that act on a uniform level of BMP-4 protein. These in turn are regulated by the activity of tolloid-related metalloproteases, such as Xenopus xolloid and zebrafish tolloid.

Khalil N, Parekh TV, O'Connor R, Antman N, Kepron W, Yehaulaeshet T, Xu YD, Gold LI. Thorax 2001 Dec;56(12):907-15 Regulation of the effects of TGF-beta1 by activation of latent TGF-beta1 and differential expression of TGF-beta receptors (TbetaR-I and TbetaR-II) in idiopathic pulmonary fibrosis.

BACKGROUND: Idiopathic pulmonary fibrosis (IPF) is characterised by subpleural fibrosis that progresses to involve all areas of the lung. The expression of transforming growth factor-beta1 (TGF-beta1), a potent regulator of connective tissue synthesis, is increased in lung sections of patients with IPF. TGF-beta1 is generally released in a biologically latent form (L-TGF-beta1). Before being biologically active, TGF-beta must be converted to its active form and interact with both TGF-beta receptors type I and II (TbetaR-I and TbetaR-II). TGF-beta latency binding protein 1 (LTBP-1), which facilitates the release and activation of L-TGF-beta1, is also important in the biology of TGF-beta1. METHODS: Open lung biopsy samples from patients with IPF and normal controls were examined to localise TbetaR-I, TbetaR-II, and LTBP-1. Alveolar macrophages (AM) and bronchoalveolar lavage (BAL) fluid were examined using the CCL-64 bioassay to determine if TGF-beta is present in its active form in the lungs of patients with IPF. RESULTS: Immunoreactive L-TGF-beta1 was present in all lung cells of patients with IPF except for fibroblasts in the subepithelial regions of honeycomb cysts. LTBP-1 was detected primarily in AM and epithelial cells lining honeycomb cysts in areas of advanced IPF. In normal lungs LTBP-1 immunoreactivity was observed in a few AM. AM from the upper and lower lobes of patients with IPF secreted 1.6 (0.6) fmol and 4.1 (1.9) fmol active TGF-beta, respectively, while AM from the lower lobes of control patients secreted no active TGF-beta (p

Roth-Eichhorn S, Heitmann B, Flemming P, Kubicka S, Trautwein C.Scand J Gastroenterol 2001 Nov;36(11):1204-10 Evidence for the decreased expression of the latent TGF-beta binding protein and its splice form in human liver tumours.

BACKGROUND: Recently, a splice form of the latent TGF-beta binding protein (LTBP-1) was identified in the liver lacking potential important sequences for matrix association and proteinase cleavage (LTBP-1D, -1delta53). For a better understanding of the unknown (patho)physiological role, the expression levels of LTBP-1D and LTBP-1 (full length) were investigated in normal and malignant human liver on the mRNA and protein level. METHODS: Normal liver (5 specimens), hepatocellular carcinoma (4 specimens) and fibrolamellar carcinoma (2 specimens) were examined by quantitative reverse transcription-polymerase chain reaction and immunohistochemistry, for which specific antibodies were generated. RESULTS: The mRNA levels of LTBP-1/-1D in malignant liver tissues are decreased in comparison to normal liver--more so in HCC than in FLC. This finding was confirmed by a strong decrease of immunostaining of LTBP-1/-1D in neoplastic parenchymal cells of HCC and FLC. However, the intensity of LTBP-1 (full length) protein staining was increased in the extracellular matrix of the carcinomas, while LTBP-1D was not detectable in the matrix. CONCLUSION: Since TGF-beta is known to be over-expressed in liver tumours, the results suggest its enhanced synthesis without binding to LTBP-1. This probably influences the availability of bioactive TGF-beta in the tumour tissue. The missing matrix localization of LTBP-1D indicates that the hinge region containing a heparin-binding site is essential for the binding of LTBP-1 in the extracellular matrix. LTBP-1D may fulfil specific functions for the latency of matrix-unbound TGF-beta.

Barcellos-Hoff MH. J Mammary Gland Biol Neoplasia 1996;1(4):353-63 Latency and activation in the control of TGF-beta.

The biological activity of the transforming growth factor-beta's (TGF-beta)3 is tightly controlled by their persistence in the extracellular compartment as latent complexes. Each of the three mammalian isoform genes encodes a product that is cleaved intracellularly to form

two polypeptides, each of which dimerizes. Mature TGF-beta, a 24 kD homodimer, is noncovalently associated with the 80 kD latency-associated peptide (LAP). LAP is a fundamental component of TGF-beta that is required for its efficient secretion, prevents it from binding to ubiquitous cell surface receptors, and maintains its availability in a large extracellular reservoir that is readily accessed by activation. This latent TGF-beta complex (LTGF-beta) is secreted by all cells and is abundant both in circulating forms and bound to the extracellular matrix. Activation describes the collective events leading to the release of TGF-beta. Despite the importance of TGF-beta regulation of growth and differentiation in physiological and malignant tissue processes, remarkably little is known about the mechanisms of activation in situ. Recent studies of irradiated mammary gland reveal certain features of TGF-beta 1 activation that may shed light on its regulation and potential roles in the normal and neoplastic mammary gland.

Barry F, Boynton RE, Liu B, Murphy JM. Exp Cell Res 2001 Aug 15;268(2):189-200 Chondrogenic differentiation of mesenchymal stem cells from bone marrow: differentiation-dependent gene expression of matrix components.

Transforming growth factor (TGF)-beta-induced chondrogenesis of mesenchymal stem cells derived from bone marrow involves the rapid deposition of a cartilage-specific extracellular matrix. The sequential events in this pathway leading from the undifferentiated stem cell to a mature chondrocyte were investigated by analysis of key matrix elements. Differentiation was rapidly induced in cells cultured in the presence of TGF-beta 3 or -beta 2 and was accompanied by the early expression of fibromodulin and cartilage oligomeric matrix protein. An increase in aggrecan and versican core protein synthesis defined an intermediate stage, which also involved the small leucine-rich proteoglycans decorin and biglycan. This was followed by the appearance of type II collagen and chondroadherin. The pathway was also characterized by the appearance of type X collagen, usually associated with hypertrophic cartilage. There was also a change in the pattern of sulfation of chondroitin sulfate, with a progressive increase in the proportion of 6-sulfated species. The major proportion of newly synthesized glycosaminoglycan was part of an aggregating proteoglycan network. These data allow us to define the phenotype of the differentiated cell and to understand in greater detail the sequential process of matrix assembly.

Lawrence DA. Mol Cell Biochem 2001 Mar;219(1-2):163-70 Latent-TGF-beta: an overview.

The latency associated with the transforming growth factor-betas (TGF-betas) was discovered in 1984. Since the two publications on this subject in that year, there has been on average over sixty reports in which latency was the dominant theme for each of the past 10 years, proof enough of the interest in this field of growth factor research. As the mature 25 kD forms of the TGF-betas are required for them to exert their many, diverse biological effects, it was inevitable that an explanation of the structure and of the activation of the latent complexes be sought. This overview provides a description of these essential points. Now that it has been clearly shown that dysregulation of particular components of the TGF-beta signalling pathway is implicated in many human diseases, the activation of the latent TGF-beta complexes has taken on added importance. Technical improvements enable the distinction of active and latent TGF-beta proteins in vivo and have started to reveal anomalies in the control of activation in relation to various pathological situations.

Fagenholz PJ, Warren SM, Greenwald JA, Bouletreau PJ, Spector JA, Crisera FE, Longaker MT. J Craniofac Surg 2001 Mar;12(2):183-90 Osteoblast gene expression is differentially regulated by TGF-beta isoforms.

The transforming growth factor beta (TGF-beta) superfamily encompasses a number of important growth factors including several TGF-beta isoforms, the bone morphogenetic proteins, activins, inhibins, and growth and differentiation factors. TGF-beta 1, -beta 2, and -

beta 3 are three closely related isoforms that are widely expressed during skeletal morphogenesis and bone repair. Numerous studies suggest that each isoform has unique in vivo functions; however, the effects of these TGF-beta isoforms on osteoblast gene expression and maturation have never been directly compared. In the current study, we treated undifferentiated neonatal rat calvaria osteoblast-enriched cell cultures with 2.5 ng/ml of each TGF-beta isoform and analyzed gene expression at 0, 3, 6, and 24 hours. We demonstrated unique isoform-specific regulation of endogenous TGF-beta 1 and type I collagen mRNA transcription. To assess the effects of extended TGF-beta treatment on osteoblast maturation, we differentiated osteoblast cultures in the presence of 2.5 ng/ml of each TGF-beta isoform. Analysis of collagen I, alkaline phosphatase, and osteocalcin demonstrated that each TGF-beta isoform uniquely suppressed the transcription of these osteoblast differentiation markers. Interestingly, TGF-beta isoform treatment increased osteopontin expression in primary osteoblasts after 4 and 10 days of differentiation. To our knowledge, these data provide the first direct comparison of the effects of the TGF-beta isoforms on osteoblast gene expression in vitro. Furthermore, these data suggest that TGF-beta isoforms may exert their unique in vivo effects by differentially regulating osteoblast cytokine secretion, extracellular matrix production, and the rate of cellular maturation.

E. NOV7 (GMAP000808_A_da1)

Expression of gene GMAP000808_A_da1 was assessed using the primer-probe set Ag2496, described in Table 17EA. Results of the RTQ-PCR runs are shown in Tables 17EB, and 17EC.

Table 17EA. Probe Name Ag2496

Primers	Sequences	Length	Start Position
Forward	5'-gcaacagcatggtgatctg-3' (SEQ ID NO: 137)	19	133
Probe	TET-5'-ctttcgaatgcacaggaacccctct-3'-TAMRA (SEQ ID NO: 138)	26	161
Reverse	5'-cgccaggttgaggatatagat-3' (SEQ ID NO: 139)	21	189

Table 17EB. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2496, Run 165639540	Tissue Name	Rel. Exp.(%) Ag2496, Run 165639540
Liver adenocarcinoma	0.0	Kidney (fetal)	11.3
Pancreas	0.0	Renal ca. 786-0	0.0
Pancreatic ca. CAPAN 2	0.0	Renal ca. A498	0.0
Adrenal gland	0.0	Renal ca. RXF 393	0.0
Thyroid	22.7	Renal ca. ACHN	0.0
Salivary gland	0.0	Renal ca. UO-31	0.0
Pituitary gland	10.5	Renal ca. TK-10	0.0
Brain (fetal)	20.3	Liver	0.0
Brain (whole)	17.9	Liver (fetal)	0.0
Brain (amygdala)	8.6	Liver ca. (hepatoblast) HepG2	0.0
Brain (cerebellum)	**100.0**	Lung	0.0
Brain (hippocampus)	22.4	Lung (fetal)	0.0
Brain (substantia nigra)	0.0	Lung ca. (small cell) LX-1	19.1

Brain (thalamus)	0.0	Lung ca. (small cell) NCI-H69	0.0
Cerebral Cortex	0.0	Lung ca. (s.cell var.) SHP-77	10.2
Spinal cord	0.0	Lung ca. (large cell)NCI-H460	45.7
glio/astro U87-MG	0.0	Lung ca. (non-sm. cell) A549	13.3
glio/astro U-118-MG	0.0	Lung ca. (non-s.cell) NCI-H23	0.0
astrocytoma SW1783	0.0	Lung ca. (non-s.cell) HOP-62	0.0
neuro*; met SK-N-AS	11.3	Lung ca. (non-s.cl) NCI-H522	0.0
astrocytoma SF-539	10.7	Lung ca. (squam.) SW 900	0.0
astrocytoma SNB-75	0.0	Lung ca. (squam.) NCI-H596	0.0
glioma SNB-19	0.0	Mammary gland	0.0
glioma U251	0.0	Breast ca.* (pl.ef) MCF-7	0.0
glioma SF-295	0.0	Breast ca.* (pl.ef) MDA-MB-231	0.0
Heart (Fetal)	0.0	Breast ca.* (pl. ef) T47D	0.0
Heart	10.1	Breast ca. BT-549	0.0
Skeletal muscle (Fetal)	0.0	Breast ca. MDA-N	0.0
Skeletal muscle	0.0	Ovary	0.0
Bone marrow	0.0	Ovarian ca. OVCAR-3	12.1
Thymus	13.3	Ovarian ca. OVCAR-4	0.0
Spleen	0.0	Ovarian ca. OVCAR-5	10.0
Lymph node	9.2	Ovarian ca. OVCAR-8	0.0
Colorectal	18.8	Ovarian ca. IGROV-1	0.0
Stomach	0.0	Ovarian ca. (ascites) SK-OV-3	0.0
Small intestine	20.3	Uterus	51.8
Colon ca. SW480	0.0	Placenta	0.0
Colon ca.* SW620 (SW480 met)	11.0	Prostate	29.9
Colon ca. HT29	0.0	Prostate ca.* (bone	0.0

		met) PC-3	
Colon ca. HCT-116	0.0	Testis	48.3
Colon ca. CaCo-2	0.0	Melanoma Hs688(A).T	0.0
CC Well to Mod Diff (ODO3866)	0.0	Melanoma* (met) Hs688(B).T	0.0
Colon ca. HCC-2998	0.0	Melanoma UACC-62	0.0
Gastric ca. (liver met) NCI-N87	9.9	Melanoma M14	0.0
Bladder	11.3	Melanoma LOX IMVI	0.0
Trachea	0.0	Melanoma* (met) SK-MEL-5	0.0
Kidney	0.0	Adipose	13.3

Table 17EC. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2496, Run 158563772	Tissue Name	Rel. Exp.(%) Ag2496, Run 158563772
Secondary Th1 act	4.9	HUVEC IL-1beta	0.0
Secondary Th2 act	7.1	HUVEC IFN gamma	2.8
Secondary Tr1 act	0.0	HUVEC TNF alpha + IFN gamma	0.0
Secondary Th1 rest	4.6	HUVEC TNF alpha + IL4	0.0
Secondary Th2 rest	11.5	HUVEC IL-11	0.0
Secondary Tr1 rest	15.2	Lung Microvascular EC none	0.0
Primary Th1 act	0.0	Lung Microvascular EC TNFalpha + IL-1beta	0.0
Primary Th2 act	0.0	Microvascular Dermal EC none	0.0
Primary Tr1 act	0.0	Microsvasular Dermal EC TNFalpha + IL-1beta	0.0
Primary Th1 rest	**100.0**	Bronchial epithelium TNFalpha + IL1beta	0.0
Primary Th2 rest	18.9	Small airway epithelium none	0.0
Primary Tr1 rest	0.0	Small airway epithelium TNFalpha + IL-1beta	0.0
CD45RA CD4 lymphocyte act	3.0	Coronery artery SMC rest	0.0
CD45RO CD4 lymphocyte act	7.7	Coronery artery SMC TNFalpha + IL-1beta	0.0
CD8 lymphocyte act	0.0	Astrocytes rest	0.0
Secondary CD8 lymphocyte rest	10.1	Astrocytes TNFalpha + IL-1beta	5.8

Secondary CD8 lymphocyte act	0.0	KU-812 (Basophil) rest	0.0
CD4 lymphocyte none	28.3	KU-812 (Basophil) PMA/ionomycin	1.8
2ry Th1/Th2/Tr1_anti-CD95 CH11	2.5	CCD1106 (Keratinocytes) none	0.0
LAK cells rest	24.0	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	0.0
LAK cells IL-2	3.1	Liver cirrhosis	19.1
LAK cells IL-2+IL-12	7.0	Lupus kidney	0.0
LAK cells IL-2+IFN gamma	19.1	NCI-H292 none	2.7
LAK cells IL-2+ IL-18	12.8	NCI-H292 IL-4	2.5
LAK cells PMA/ionomycin	0.0	NCI-H292 IL-9	2.6
NK Cells IL-2 rest	0.0	NCI-H292 IL-13	3.9
Two Way MLR 3 day	7.7	NCI-H292 IFN gamma	0.0
Two Way MLR 5 day	0.0	HPAEC none	0.0
Two Way MLR 7 day	0.0	HPAEC TNF alpha + IL-1 beta	0.0
PBMC rest	6.3	Lung fibroblast none	0.0
PBMC PWM	2.6	Lung fibroblast TNF alpha + IL-1 beta	2.1
PBMC PHA-L	5.8	Lung fibroblast IL-4	0.0
Ramos (B cell) none	0.0	Lung fibroblast IL-9	0.0
Ramos (B cell) ionomycin	0.0	Lung fibroblast IL-13	0.0
B lymphocytes PWM	2.8	Lung fibroblast IFN gamma	0.0
B lymphocytes CD40L and IL-4	7.6	Dermal fibroblast CCD1070 rest	0.0
EOL-1 dbcAMP	0.0	Dermal fibroblast CCD1070 TNF alpha	9.7
EOL-1 dbcAMP PMA/ionomycin	2.5	Dermal fibroblast CCD1070 IL-1 beta	0.0
Dendritic cells none	0.0	Dermal fibroblast IFN gamma	1.9
Dendritic cells LPS	0.0	Dermal fibroblast IL-4	0.0
Dendritic cells anti-CD40	0.0	IBD Colitis 2	0.0
Monocytes rest	4.6	IBD Crohn's	6.4
Monocytes LPS	0.0	Colon	13.2
Macrophages rest	0.0	Lung	18.6
Macrophages LPS	0.0	Thymus	9.2
HUVEC none	0.0	Kidney	24.0

HUVEC starved	0.0		

CNS_neurodegeneration_v1.0 Summary: Ag2496 Expression is low/undetected in all samples in this panel (CT>35). (Data not shown.)

Panel 1.3D Summary: Ag2496 This gene appears to be specific to the cerebellum, and thus expression of this gene could be used to distinguish cerebellar tissue from other CNS tissue. Furthermore therapeutic modulation of the expression or function of this gene product may be of use in treating diseases which show a primary pathology in this region (spinocerebellar ataxia).

Panel 4D Summary: This transcript is most highly expressed (CT=31.5) in resting effector Th1 T cells and not in the corresponding activated cells. Thus, this gene may be a useful marker for Th1 cells. This gene is also expressed at a lower level in resting CD4 T cells and LAK cells. Therefore, small molecule antagonists that block the function of this encoded protein may be useful for treatment of Th1-mediated diseases such inflammatory bowel disease, rheumatoid arthritis, and other autoimmune diseases, such as delayed type hypersensitivity reactions. This transcript is also expressed at significant levels in kidney and thus could potentially serve as a marker for kidney tissue

F. NOV8 (AL163195_da2)

Expression of gene AL163195_da2_ was assessed using the primer-probe set Ag2477, described in Table 18FA. Results of the RTQ-PCR runs are shown in Tables 18FB and 18FC.

Table 18FA. Probe Name Ag2477

Primers	Sequences	Length	Start Position
Forward	5'-ctgcaaccacatgatcatacaa-3' (SEQ ID NO: 140)	22	158
Probe	TET-5'-atcagggaacctgaccacacttgtaa-3'-TAMRA (SEQ ID NO: 141)	26	186
Reverse	5'-atggatgaagacatgctccttt-3' (SEQ ID NO: 142)	22	212

Table 18FB. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2477, Run 165639391	Tissue Name	Rel. Exp.(%) Ag2477, Run 165639391
Liver adenocarcinoma	0.0	Kidney (fetal)	0.0
Pancreas	0.0	Renal ca. 786-0	0.0
Pancreatic ca. CAPAN 2	0.0	Renal ca. A498	0.0
Adrenal gland	0.0	Renal ca. RXF 393	0.0
Thyroid	0.0	Renal ca. ACHN	0.0
Salivary gland	0.0	Renal ca. UO-31	0.0
Pituitary gland	0.0	Renal ca. TK-10	0.0
Brain (fetal)	0.0	Liver	0.0
Brain (whole)	0.0	Liver (fetal)	0.0
Brain (amygdala)	0.0	Liver ca. (hepatoblast) HepG2	0.0
Brain (cerebellum)	0.0	Lung	0.0
Brain (hippocampus)	0.0	Lung (fetal)	0.0
Brain (substantia nigra)	0.0	Lung ca. (small cell)	0.0

		LX-1	
Brain (thalamus)	0.0	Lung ca. (small cell) NCI-H69	0.0
Cerebral Cortex	0.0	Lung ca. (s.cell var.) SHP-77	18.8
Spinal cord	0.0	Lung ca. (large cell)NCI-H460	0.0
glio/astro U87-MG	0.0	Lung ca. (non-sm. cell) A549	0.0
glio/astro U-118-MG	0.0	Lung ca. (non-s.cell) NCI-H23	0.0
astrocytoma SW1783	0.0	Lung ca. (non-s.cell) HOP-62	0.0
neuro*; met SK-N-AS	0.0	Lung ca. (non-s.cl) NCI-H522	0.0
astrocytoma SF-539	0.0	Lung ca. (squam.) SW 900	0.0
astrocytoma SNB-75	0.0	Lung ca. (squam.) NCI-H596	0.0
glioma SNB-19	0.0	Mammary gland	0.0
glioma U251	7.5	Breast ca.* (pl.ef) MCF-7	0.0
glioma SF-295	13.7	Breast ca.* (pl.ef) MDA-MB-231	0.0
Heart (Fetal)	0.0	Breast ca.* (pl. ef) T47D	0.0
Heart	0.0	Breast ca. BT-549	0.0
Skeletal muscle (Fetal)	0.0	Breast ca. MDA-N	0.0
Skeletal muscle	0.0	Ovary	0.0
Bone marrow	0.0	Ovarian ca. OVCAR-3	0.0
Thymus	0.0	Ovarian ca. OVCAR-4	0.0
Spleen	0.0	Ovarian ca. OVCAR-5	0.0
Lymph node	0.0	Ovarian ca. OVCAR-8	0.0
Colorectal	0.0	Ovarian ca. IGROV-1	0.0
Stomach	0.0	Ovarian ca. (ascites) SK-OV-3	0.0
Small intestine	0.0	Uterus	0.0
Colon ca. SW480	0.0	Placenta	0.0
Colon ca.* SW620 (SW480 met)	0.0	Prostate	0.0

Colon ca. HT29	0.0	Prostate ca.* (bone met) PC-3	0.0
Colon ca. HCT-116	0.0	Testis	**100.0**
Colon ca. CaCo-2	0.0	Melanoma Hs688(A).T	0.0
CC Well to Mod Diff (ODO3866)	0.0	Melanoma* (met) Hs688(B).T	0.0
Colon ca. HCC-2998	0.0	Melanoma UACC-62	0.0
Gastric ca. (liver met) NCI-N87	0.0	Melanoma M14	0.0
Bladder	0.0	Melanoma LOX IMVI	0.0
Trachea	9.1	Melanoma* (met) SK-MEL-5	0.0
Kidney	0.0	Adipose	0.0

Table 18FC. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2477, Run 164391869	Tissue Name	Rel. Exp.(%) Ag2477, Run 164391869
Secondary Th1 act	0.0	HUVEC IL-1beta	0.0
Secondary Th2 act	0.0	HUVEC IFN gamma	0.0
Secondary Tr1 act	0.0	HUVEC TNF alpha + IFN gamma	0.0
Secondary Th1 rest	0.0	HUVEC TNF alpha + IL4	0.0
Secondary Th2 rest	0.0	HUVEC IL-11	0.0
Secondary Tr1 rest	0.0	Lung Microvascular EC none	0.0
Primary Th1 act	35.8	Lung Microvascular EC TNFalpha + IL-1beta	0.0
Primary Th2 act	0.0	Microvascular Dermal EC none	0.0
Primary Tr1 act	0.0	Microsvasular Dermal EC TNFalpha + IL-1beta	0.0
Primary Th1 rest	0.0	Bronchial epithelium TNFalpha + IL1beta	0.0
Primary Th2 rest	0.0	Small airway epithelium none	0.0
Primary Tr1 rest	0.0	Small airway epithelium TNFalpha + IL-1beta	0.0
CD45RA CD4 lymphocyte act	0.0	Coronery artery SMC rest	0.0
CD45RO CD4 lymphocyte act	0.0	Coronery artery SMC TNFalpha + IL-1beta	0.0
CD8 lymphocyte act	0.0	Astrocytes rest	0.0
Secondary CD8	0.0	Astrocytes TNFalpha +	0.0

lymphocyte rest		IL-1beta	
Secondary CD8 lymphocyte act	0.0	KU-812 (Basophil) rest	0.0
CD4 lymphocyte none	0.0	KU-812 (Basophil) PMA/ionomycin	0.0
2ry Th1/Th2/Tr1_anti-CD95 CH11	0.0	CCD1106 (Keratinocytes) none	0.0
LAK cells rest	0.0	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	0.0
LAK cells IL-2	17.0	Liver cirrhosis	**100.0**
LAK cells IL-2+IL-12	0.0	Lupus kidney	0.0
LAK cells IL-2+IFN gamma	0.0	NCI-H292 none	0.0
LAK cells IL-2+ IL-18	0.0	NCI-H292 IL-4	0.0
LAK cells PMA/ionomycin	0.0	NCI-H292 IL-9	0.0
NK Cells IL-2 rest	0.0	NCI-H292 IL-13	0.0
Two Way MLR 3 day	0.0	NCI-H292 IFN gamma	0.0
Two Way MLR 5 day	0.0	HPAEC none	0.0
Two Way MLR 7 day	0.0	HPAEC TNF alpha + IL-1 beta	0.0
PBMC rest	0.0	Lung fibroblast none	0.0
PBMC PWM	0.0	Lung fibroblast TNF alpha + IL-1 beta	0.0
PBMC PHA-L	0.0	Lung fibroblast IL-4	0.0
Ramos (B cell) none	0.0	Lung fibroblast IL-9	0.0
Ramos (B cell) ionomycin	0.0	Lung fibroblast IL-13	0.0
B lymphocytes PWM	0.0	Lung fibroblast IFN gamma	0.0
B lymphocytes CD40L and IL-4	0.0	Dermal fibroblast CCD1070 rest	0.0
EOL-1 dbcAMP	0.0	Dermal fibroblast CCD1070 TNF alpha	0.0
EOL-1 dbcAMP PMA/ionomycin	0.0	Dermal fibroblast CCD1070 IL-1 beta	0.0
Dendritic cells none	0.0	Dermal fibroblast IFN gamma	10.3
Dendritic cells LPS	0.0	Dermal fibroblast IL-4	0.0
Dendritic cells anti-CD40	0.0	IBD Colitis 2	22.8
Monocytes rest	0.0	IBD Crohn's	0.0
Monocytes LPS	0.0	Colon	0.0
Macrophages rest	0.0	Lung	0.0
Macrophages LPS	0.0	Thymus	8.0

HUVEC none	0.0	Kidney	0.0
HUVEC starved	0.0		

Panel 1.3D Summary: Ag2477 Significant expression of this gene is restricted to the testis (CT=33.1). Thus, expression of this gene could be used to differentiate testis tissue from other tissues. Furthermore, the highly specific expression of this gene suggests that its protein product may be involved in the normal function of the testis. Thus, therapeutic modulation of the expression or function of this gene may be useful in the treatment of infertility and other disorders that involve the testis.

Panel 4D Summary: Ag 2477 This transcript is expressed almost exclusively in liver cirrhosis (CT=33.5) but not in normal liver. This suggests that the protein encoded by this transcript may be involved or associated with the pathology of the liver and may serve as a diagnostic marker for liver cirrhosis or other inflammatory liver diseases.

G. CG58610-01/SC87421058_A: AMINOTRANSFERASE

Expression of gene CG58610-01 was assessed using the primer-probe set Ag2267, described in Table 19GA.

Table 19GA. Probe Name Ag2267

Primers	Sequences	Length	Start Position
Forward	5'-caattttggttctggagaaaga-3' (SEQ ID NO: 143)	22	1218
Probe	TET-5'-tctcagtgccgatggacctcatagaa-3'-TAMRA (SEQ ID NO: 144)	26	1252
Reverse	5'-cagtgaagcacataggtggttt-3' (SEQ ID NO: 145)	22	1292

CNS_neurodegeneration_v1.0 Summary: Ag2267 Expression is low/undetectable in all samples in this panel (CTs>35). (Data not shown.)

Panel 1.3D Summary: Ag2267 Expression is low/undetectable in all samples in this panel (CTs>35). (Data not shown.)

Panel 2D Summary: Ag2267 Expression is low/undetectable in all samples in this panel (CTs>35). (Data not shown.)

Panel 4D Summary: Ag2267 Expression is low/undetectable in all samples in this panel (CTs>35). (Data not shown.)

H. NOV10a (CG50235-01)

Expression of gene CG50235-01 was assessed using the primer-probe set Ag4737, described in Table20HA. Results of the RTQ-PCR runs are shown in Tables 20HB, 20HC, and 20HD.

Table 20HA. Probe Name Ag4737

Primers	Sequences	Length	Start Position
Forward	5'-ctgggagagacatacgactttg-3' (SEQ ID NO: 146)	22	1229
Probe	TET-5'-cccggaacaccttctcaagaggagt-3'-TAMRA (SEQ ID NO: 147)	25	1269
Reverse	5'-gggaaggatggtgtctaagaaa-3' (SEQ ID NO: 148)	22	1294

Table 20HB. CNS_neurodegeneration_v1.0

Tissue Name	Rel. Exp.(%) Ag4737, Run 224721331	Tissue Name	Rel. Exp.(%) Ag4737, Run 224721331
AD 1 Hippo	23.3	Control (Path) 3	4.5

		Temporal Ctx	
AD 2 Hippo	36.6	Control (Path) 4 Temporal Ctx	11.0
AD 3 Hippo	31.4	AD 1 Occipital Ctx	21.9
AD 4 Hippo	9.3	AD 2 Occipital Ctx (Missing)	0.0
AD 5 Hippo	38.4	AD 3 Occipital Ctx	25.7
AD 6 Hippo	15.2	AD 4 Occipital Ctx	38.7
Control 2 Hippo	39.8	AD 5 Occipital Ctx	63.3
Control 4 Hippo	30.1	AD 5 Occipital Ctx	23.0
Control (Path) 3 Hippo	20.3	Control 1 Occipital Ctx	4.7
AD 1 Temporal Ctx	38.7	Control 2 Occipital Ctx	41.5
AD 2 Temporal Ctx	74.2	Control 3 Occipital Ctx	20.4
AD 3 Temporal Ctx	8.1	Control 4 Occipital Ctx	18.2
AD 4 Temporal Ctx	32.8	Control (Path) 1 Occipital Ctx	84.1
AD 5 Inf Temporal Ctx	**100.0**	Control (Path) 2 Occipital Ctx	13.3
AD 5 Sup Temporal Ctx	48.6	Control (Path) 3 Occipital Ctx	4.6
AD 6 Inf Temporal Ctx	13.1	Control (Path) 4 Occipital Ctx	5.0
AD 6 Sup Temporal Ctx	22.7	Control 1 Parietal Ctx	14.1
Control 1 Temporal Ctx	5.1	Control 2 Parietal Ctx	38.7
Control 2 Temporal Ctx	62.0	Control 3 Parietal Ctx	36.9
Control 3 Temporal Ctx	39.8	Control (Path) 1 Parietal Ctx	38.7
Control 3 Temporal Ctx	31.4	Control (Path) 2 Parietal Ctx	55.5
Control (Path) 1 Temporal Ctx	43.8	Control (Path) 3 Parietal Ctx	0.0
Control (Path) 2 Temporal Ctx	14.1	Control (Path) 4 Parietal Ctx	5.1

Table 20HC. General_screening_panel_v1.4

Tissue Name	Rel. Exp.(%) Ag4737, Run 222904895	Tissue Name	Rel. Exp.(%) Ag4737, Run 222904895
Adipose	0.0	Renal ca. TK-10	1.1
Melanoma*	4.3	Bladder	6.8

Hs688(A).T			
Melanoma* Hs688(B).T	1.3	Gastric ca. (liver met.) NCI-N87	5.2
Melanoma* M14	0.0	Gastric ca. KATO III	2.0
Melanoma* LOXIMVI	0.0	Colon ca. SW-948	0.0
Melanoma* SK-MEL-5	1.0	Colon ca. SW480	9.9
Squamous cell carcinoma SCC-4	7.3	Colon ca.* (SW480 met) SW620	0.3
Testis Pool	0.9	Colon ca. HT29	0.0
Prostate ca.* (bone met) PC-3	0.5	Colon ca. HCT-116	8.6
Prostate Pool	5.6	Colon ca. CaCo-2	0.5
Placenta	2.0	Colon cancer tissue	0.5
Uterus Pool	0.8	Colon ca. SW1116	16.2
Ovarian ca. OVCAR-3	9.1	Colon ca. Colo-205	1.1
Ovarian ca. SK-OV-3	67.8	Colon ca. SW-48	0.0
Ovarian ca. OVCAR-4	88.3	Colon Pool	0.0
Ovarian ca. OVCAR-5	0.0	Small Intestine Pool	6.9
Ovarian ca. IGROV-1	6.6	Stomach Pool	1.2
Ovarian ca. OVCAR-8	8.7	Bone Marrow Pool	0.0
Ovary	3.3	Fetal Heart	26.1
Breast ca. MCF-7	0.8	Heart Pool	21.9
Breast ca. MDA-MB-231	1.1	Lymph Node Pool	1.6
Breast ca. BT 549	0.0	Fetal Skeletal Muscle	2.7
Breast ca. T47D	3.1	Skeletal Muscle Pool	17.3
Breast ca. MDA-N	0.0	Spleen Pool	2.4
Breast Pool	0.3	Thymus Pool	1.4
Trachea	5.5	CNS cancer (glio/astro) U87-MG	0.0
Lung	0.9	CNS cancer (glio/astro) U-118-MG	0.0
Fetal Lung	0.5	CNS cancer (neuro;met) SK-N-AS	2.9
Lung ca. NCI-N417	0.0	CNS cancer (astro) SF-539	0.5
Lung ca. LX-1	0.5	CNS cancer (astro)	1.4

		SNB-75	
Lung ca. NCI-H146	0.9	CNS cancer (glio) SNB-19	5.3
Lung ca. SHP-77	44.4	CNS cancer (glio) SF-295	0.0
Lung ca. A549	0.9	Brain (Amygdala) Pool	7.8
Lung ca. NCI-H526	54.7	Brain (cerebellum)	3.6
Lung ca. NCI-H23	8.8	Brain (fetal)	1.1
Lung ca. NCI-H460	0.3	Brain (Hippocampus) Pool	7.2
Lung ca. HOP-62	0.0	Cerebral Cortex Pool	5.6
Lung ca. NCI-H522	8.0	Brain (Substantia nigra) Pool	19.2
Liver	0.5	Brain (Thalamus) Pool	18.0
Fetal Liver	2.0	Brain (whole)	6.3
Liver ca. HepG2	1.0	Spinal Cord Pool	42.0
Kidney Pool	1.4	Adrenal Gland	0.0
Fetal Kidney	1.2	Pituitary gland Pool	7.8
Renal ca. 786-0	**100.0**	Salivary Gland	7.4
Renal ca. A498	17.0	Thyroid (female)	1.8
Renal ca. ACHN	45.1	Pancreatic ca. CAPAN2	0.0
Renal ca. UO-31	82.9	Pancreas Pool	2.8

Table 20HD. Panel 4.1D

Tissue Name	Rel. Exp.(%) Ag4737, Run 204154022	Tissue Name	Rel. Exp.(%) Ag4737, Run 204154022
Secondary Th1 act	0.0	HUVEC IL-1beta	0.0
Secondary Th2 act	0.0	HUVEC IFN gamma	3.3
Secondary Tr1 act	0.0	HUVEC TNF alpha + IFN gamma	0.0
Secondary Th1 rest	0.0	HUVEC TNF alpha + IL4	0.0
Secondary Th2 rest	0.0	HUVEC IL-11	0.0
Secondary Tr1 rest	0.0	Lung Microvascular EC none	0.0
Primary Th1 act	0.0	Lung Microvascular EC TNFalpha + IL-1beta	0.0
Primary Th2 act	2.5	Microvascular Dermal EC none	0.0
Primary Tr1 act	0.0	Microsvasular Dermal EC TNFalpha + IL-1beta	0.0
Primary Th1 rest	0.0	Bronchial epithelium TNFalpha + IL1beta	39.8
Primary Th2 rest	0.0	Small airway epithelium none	43.2

Primary Tr1 rest	0.0	Small airway epithelium TNFalpha + IL-1beta	12.3
CD45RA CD4 lymphocyte act	0.0	Coronery artery SMC rest	0.0
CD45RO CD4 lymphocyte act	0.0	Coronery artery SMC TNFalpha + IL-1beta	0.0
CD8 lymphocyte act	0.0	Astrocytes rest	73.7
Secondary CD8 lymphocyte rest	0.0	Astrocytes TNFalpha + IL-1beta	**100.0**
Secondary CD8 lymphocyte act	0.0	KU-812 (Basophil) rest	0.0
CD4 lymphocyte none	0.0	KU-812 (Basophil) PMA/ionomycin	2.7
2ry Th1/Th2/Tr1_anti-CD95 CH11	0.0	CCD1106 (Keratinocytes) none	29.5
LAK cells rest	0.0	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	5.6
LAK cells IL-2	0.0	Liver cirrhosis	0.0
LAK cells IL-2+IL-12	0.0	NCI-H292 none	12.5
LAK cells IL-2+IFN gamma	0.0	NCI-H292 IL-4	0.0
LAK cells IL-2+ IL-18	0.0	NCI-H292 IL-9	11.3
LAK cells PMA/ionomycin	0.0	NCI-H292 IL-13	0.0
NK Cells IL-2 rest	0.0	NCI-H292 IFN gamma	0.0
Two Way MLR 3 day	0.0	HPAEC none	0.0
Two Way MLR 5 day	0.0	HPAEC TNF alpha + IL-1 beta	2.9
Two Way MLR 7 day	0.0	Lung fibroblast none	0.0
PBMC rest	0.0	Lung fibroblast TNF alpha + IL-1 beta	0.0
PBMC PWM	3.6	Lung fibroblast IL-4	0.0
PBMC PHA-L	0.0	Lung fibroblast IL-9	4.9
Ramos (B cell) none	3.0	Lung fibroblast IL-13	0.0
Ramos (B cell) ionomycin	2.4	Lung fibroblast IFN gamma	3.4
B lymphocytes PWM	0.0	Dermal fibroblast CCD1070 rest	0.0
B lymphocytes CD40L and IL-4	3.1	Dermal fibroblast CCD1070 TNF alpha	0.0
EOL-1 dbcAMP	0.0	Dermal fibroblast CCD1070 IL-1 beta	0.0
EOL-1 dbcAMP PMA/ionomycin	0.0	Dermal fibroblast IFN gamma	0.0
Dendritic cells none	2.7	Dermal fibroblast IL-4	0.0

Dendritic cells LPS	0.0	Dermal Fibroblasts rest	0.0
Dendritic cells anti-CD40	0.0	Neutrophils TNFa+LPS	0.0
Monocytes rest	0.0	Neutrophils rest	0.0
Monocytes LPS	0.0	Colon	4.1
Macrophages rest	0.0	Lung	0.0
Macrophages LPS	0.0	Thymus	2.5
HUVEC none	0.0	Kidney	2.7
HUVEC starved	0.0		

CNS_neurodegeneration_v1.0 Summary: Ag4737 Panel CNS_Neurodegeneration does not show any difference in the expression of this gene between the postmortem brains of controls or Alzheimer's disease patients. This panel does, however, confirm the expression of this gene at low levels in the brains of an independent group of patients. See General_screening_panel_v1.4 for discussion of utility in the central nervous system.

General_screening_panel_v1.4 Summary: Ag4737 The expression of this gene appears to be highest in a sample derived from a renal cancer cell line (CT=29.9). Overall, there appears to be specific expression restricted to cell lines derived from renal cancer, ovarian cancer and lung cancer. Thus, the expression of this gene could be used to distinguish these cell lines from other samples in the panel. Moreover, therapeutic modulation of this gene, through the used of small molecule drugs, antibodies or protein therapeutics could be of benefit in the treatment of renal, ovarian or lung cancer.

This gene is also moderately expressed in several metabolic tissues including adult and fetal heart, pituitary, and skeletal muscle. Thus, this gene product may be important for the pathogenesis, diagnosis and/or treatment of metabolic diseases, including obesity. In addition, this gene appears to be differentially expressed in fetal (CT value = 35) versus adult skeletal muscle (CT value = 33), and may be useful for the differentiation of the adult vs fetal source of this tissue.

This gene is expressed at low levels in the CNS, except in the spinal cord where expression levels are moderate. Thus, this gene may be of use in treating conditions where the spinal cord is damaged such as spinal cord trauma or spinocerebellar ataxia.

Panel 4.1D Summary: Ag 4737 This transcript is most highly expressed in TNF-a and IL-1 b treated astrocytes (CT=31.9) and is expressed at a lower level in resting astrocytes (CT 32.3). This gene is also expressed at a low level in small airway epithelium and keratinocytes, with expression down regulated in both cell types upon treatment with the inflammatory cytokines TNF-a and IL-1b. This transcript encodes a tolloid like 2 protein, a BMP-1-related proteinase, which has been shown to play a role in extracellular matrix biosynthesis. Therefore, this gene product may be useful as a protein therapeutic to reduce or eliminate the symptoms of inflammatory reactions that occur in multiple sclerosis, chronic obstructive pulmonary disease, asthma, emphysema, and inflammatory skin diseases.

Reference:

Uzel MI, Scott IC, Babakhanlou-Chase H, Palamakumbura AH, Pappano WN, Hong HH, Greenspan DS, Trackman PC. J Biol Chem 2001 Jun 22;276(25):22537-43 Multiple bone morphogenetic protein 1-related mammalian metalloproteinases process pro-lysyl oxidase at the correct physiological site and control lysyl oxidase activation in mouse embryo fibroblast cultures.

Lysyl oxidase catalyzes the final enzymatic step required for collagen and elastin cross-linking in extracellular matrix biosynthesis. Pro-lysyl oxidase is processed by procollagen C-

proteinase activity, which also removes the C-propeptides of procollagens I-III. The Bmp1 gene encodes two procollagen C-proteinases: bone morphogenetic protein 1 (BMP-1) and mammalian Tolloid (mTLD). Mammalian Tolloid-like (mTLL)-1 and -2 are two genetically distinct BMP-1-related proteinases, and mTLL-1 has been shown to have procollagen C-proteinase activity. The present study is the first to directly compare pro-lysyl oxidase processing by these four related proteinases. In vitro assays with purified recombinant enzymes show that all four proteinases productively cleave pro-lysyl oxidase at the correct physiological site but that BMP-1 is 3-, 15-, and 20-fold more efficient than mTLL-1, mTLL-2, and mTLD, respectively. To more directly assess the roles of BMP-1 and mTLL-1 in lysyl oxidase activation by connective tissue cells, fibroblasts cultured from Bmp1-null, Tll1-null, and Bmp1/Tll1 double null mouse embryos, thus lacking BMP-1/mTLD, mTLL-1, or all three enzymes, respectively, were assayed for lysyl oxidase enzyme activity and for accumulation of pro-lysyl oxidase and mature approximately 30-kDa lysyl oxidase. Wild type cells or cells singly null for Bmp1 or Tll1 all produced both pro-lysyl oxidase and processed lysyl oxidase at similar levels, indicating apparently normal levels of processing, consistent with enzyme activity data. In contrast, double null Bmp1/Tll1 cells produced predominantly unprocessed 50-kDa pro-lysyl oxidase and had lysyl oxidase enzyme activity diminished by 70% compared with wild type, Bmp1-null, and Tll1-null cells. Thus, the combination of BMP-1/mTLD and mTLL-1 is shown to be responsible for the majority of processing leading to activation of lysyl oxidase by murine embryonic fibroblasts, whereas in vitro studies identify pro-lysyl oxidase as the first known substrate for mTLL-2.

Panel CNS_1.1 Summary: Ag4737 Expression is low/undetected in all the samples on this panel (CTs>35). (Data not shown.)

I. NOV10b (CG50235-03)

Expression of gene CG50235-03 was assessed using the primer-probe set Ag5112, described in Table 21IA. Results of the RTQ-PCR runs are shown in Table 21IB.

Table 21IA. Probe Name Ag5112

Primers	Sequences	Length	Start Position
Forward	5'-tgtgcttttgttagccaga-3' (SEQ ID NO: 149)	19	1127
Probe	TET-5'-catcaatctgcttgctacacttctcacca-3'-TAMRA (SEQ ID NO: 150)	29	1149
Reverse	5'-ccaaagccctcggaac-3' (SEQ ID NO: 151)	16	1182

Table 21IB. Panel 4.1D

Tissue Name	Rel. Exp.(%) Ag5112, Run 225787031	Tissue Name	Rel. Exp.(%) Ag5112, Run 225787031
Secondary Th1 act	0.0	HUVEC IL-1beta	0.0
Secondary Th2 act	0.0	HUVEC IFN gamma	0.0
Secondary Tr1 act	0.0	HUVEC TNF alpha + IFN gamma	0.0
Secondary Th1 rest	0.0	HUVEC TNF alpha + IL4	0.0
Secondary Th2 rest	0.0	HUVEC IL-11	0.6
Secondary Tr1 rest	0.0	Lung Microvascular EC none	0.0
Primary Th1 act	0.0	Lung Microvascular EC TNFalpha + IL-1beta	0.8

Primary Th2 act	0.0	Microvascular Dermal EC none	0.0
Primary Tr1 act	0.0	Microsvasular Dermal EC TNFalpha + IL-1beta	0.0
Primary Th1 rest	0.0	Bronchial epithelium TNFalpha + IL1beta	1.2
Primary Th2 rest	0.0	Small airway epithelium none	0.0
Primary Tr1 rest	0.0	Small airway epithelium TNFalpha + IL-1beta	0.3
CD45RA CD4 lymphocyte act	0.0	Coronery artery SMC rest	0.0
CD45RO CD4 lymphocyte act	0.0	Coronery artery SMC TNFalpha + IL-1beta	0.0
CD8 lymphocyte act	0.0	Astrocytes rest	1.4
Secondary CD8 lymphocyte rest	0.0	Astrocytes TNFalpha + IL-1beta	0.4
Secondary CD8 lymphocyte act	0.0	KU-812 (Basophil) rest	0.0
CD4 lymphocyte none	0.0	KU-812 (Basophil) PMA/ionomycin	0.0
2ry Th1/Th2/Tr1_anti-CD95 CH11	0.0	CCD1106 (Keratinocytes) none	0.8
LAK cells rest	0.4	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	0.3
LAK cells IL-2	0.0	Liver cirrhosis	0.0
LAK cells IL-2+IL-12	0.0	NCI-H292 none	0.0
LAK cells IL-2+IFN gamma	0.0	NCI-H292 IL-4	0.0
LAK cells IL-2+ IL-18	0.0	NCI-H292 IL-9	0.0
LAK cells PMA/ionomycin	0.0	NCI-H292 IL-13	0.0
NK Cells IL-2 rest	0.0	NCI-H292 IFN gamma	0.0
Two Way MLR 3 day	0.0	HPAEC none	0.3
Two Way MLR 5 day	0.0	HPAEC TNF alpha + IL-1 beta	0.0
Two Way MLR 7 day	0.0	Lung fibroblast none	0.0
PBMC rest	0.0	Lung fibroblast TNF alpha + IL-1 beta	0.0
PBMC PWM	0.0	Lung fibroblast IL-4	0.0
PBMC PHA-L	0.0	Lung fibroblast IL-9	0.0
Ramos (B cell) none	0.0	Lung fibroblast IL-13	0.0
Ramos (B cell) ionomycin	0.0	Lung fibroblast IFN gamma	0.0
B lymphocytes PWM	0.0	Dermal fibroblast	0.0

		CCD1070 rest	
B lymphocytes CD40L and IL-4	0.0	Dermal fibroblast CCD1070 TNF alpha	0.0
EOL-1 dbcAMP	0.0	Dermal fibroblast CCD1070 IL-1 beta	0.0
EOL-1 dbcAMP PMA/ionomycin	0.0	Dermal fibroblast IFN gamma	0.0
Dendritic cells none	0.0	Dermal fibroblast IL-4	0.0
Dendritic cells LPS	0.0	Dermal Fibroblasts rest	0.0
Dendritic cells anti-CD40	0.0	Neutrophils TNFa+LPS	0.0
Monocytes rest	0.0	Neutrophils rest	0.6
Monocytes LPS	0.6	Colon	0.7
Macrophages rest	0.0	Lung	1.9
Macrophages LPS	0.0	Thymus	16.8
HUVEC none	0.0	Kidney	**100.0**
HUVEC starved	0.0		

CNS_neurodegeneration_v1.0 Summary: Ag5112 Expression is low/undetectable in all the samples in this panel (CTs>35). (Data not shown.)

General_screening_panel_v1.5 Summary: Ag5112 Expression is low/undetectable in all the samples in this panel (CTs>35). (Data not shown.)

Panel 4.1D Summary: Ag 5112: This transcript is expressed almost exclusively in kidney (CT 31.5) and the thymus (CT 34). The transcript encoded by this transcript could be used for detection of kidney and kidney tissues. The putative protein encoded by this transcript may also play an important role in the normal homeostasis of these tissues. Therapeutics designed with the protein encoded for by this transcript could be important for maintaining or restoring normal function to these organs during inflammation

J. NOV11 (CG55748-01)

Expression of gene CG55748-01 was assessed using the primer-probe set Ag2230, described in Table 22JA.

Table 22JA. Probe Name Ag2230

Primers	Sequences	Length	Start Position
Forward	5'-tgtcgggatgtcatacactaca-3' (SEQ ID NO: 152)	22	280
Probe	TET-5'-tgtcaaaacagaccacccaagatttt-3'-TAMRA (SEQ ID NO: 153)	26	303
Reverse	5'-atcaagtccagcatacaattgg-3' (SEQ ID NO: 154)	22	333

CNS_neurodegeneration_v1.0 Summary: Ag2230 Expression is low/undetectable in all samples in this panel (CTs>35). (Data not shown.)

Panel 1.3D Summary: Ag2230 Expression is low/undetectable in all samples in this panel (CTs>35). (Data not shown.)

Panel 2D Summary: Ag2230 Expression is low/undetectable in all samples in this panel (CTs>35). (Data not shown.)

Panel 4D Summary: Ag2230 Expression is low/undetectable in all samples in this panel (CTs>35). (Data not shown.)

Example 3. SNP analysis of NOVX clones

SeqCallingTM Technology: cDNA was derived from various human samples representing multiple tissue types, normal and diseased states, physiological states, and developmental states from different donors. Samples were obtained as whole tissue, cell lines, primary cells or tissue cultured primary cells and cell lines. Cells and cell lines may have been treated with biological or chemical agents that regulate gene expression for example, growth factors, chemokines, steroids. The cDNA thus derived was then sequenced using CuraGen's proprietary SeqCalling technology. Sequence traces were evaluated manually and edited for corrections if appropriate. cDNA sequences from all samples were assembled with themselves and with public ESTs using bioinformatics programs to generate CuraGen's human SeqCalling database of SeqCalling assemblies. Each assembly contains one or more overlapping cDNA sequences derived from one or more human samples. Fragments and ESTs were included as components for an assembly when the extent of identity with another component of the assembly was at least 95% over 50 bp. Each assembly can represent a gene and/or its variants such as splice forms and/or single nucleotide polymorphisms (SNPs) and their combinations.

Variant sequences are included in this application. A variant sequence can include a single nucleotide polymorphism (SNP). A SNP can, in some instances, be referred to as a "cSNP" to denote that the nucleotide sequence containing the SNP originates as a cDNA. A SNP can arise in several ways. For example, a SNP may be due to a substitution of one nucleotide for another at the polymorphic site. Such a substitution can be either a transition or a transversion. A SNP can also arise from a deletion of a nucleotide or an insertion of a nucleotide, relative to a reference allele. In this case, the polymorphic site is a site at which one allele bears a gap with respect to a particular nucleotide in another allele. SNPs occurring within genes may result in an alteration of the amino acid encoded by the gene at the position of the SNP. Intragenic SNPs may also be silent, however, in the case that a codon including a SNP encodes the same amino acid as a result of the redundancy of the genetic code. SNPs occurring outside the region of a gene, or in an intron within a gene, do not result in changes in any amino acid sequence of a protein but may result in altered regulation of the expression pattern for example, alteration in temporal expression, physiological response regulation, cell type expression regulation, intensity of expression, stability of transcribed message.

Method of novel SNP Identification: SNPs are identified by analyzing sequence assemblies using CuraGen's proprietary SNPTool algorithm. SNPTool identifies variation in

assemblies with the following criteria: SNPs are not analyzed within 10 base pairs on both ends of an alignment; Window size (number of bases in a view) is 10; The allowed number of mismatches in a window is 2; Minimum SNP base quality (PHRED score) is 23; Minimum number of changes to score an SNP is 2/assembly position. SNPTool analyzes the assembly and displays SNP positions, associated individual variant sequences in the assembly, the depth of the assembly at that given position, the putative assembly allele frequency, and the SNP sequence variation. Sequence traces are then selected and brought into view for manual validation. The consensus assembly sequence is imported into CuraTools along with variant sequence changes to identify potential amino acid changes resulting from the SNP sequence variation. Comprehensive SNP data analysis is then exported into the SNPCalling database.

Method of novel SNP Confirmation: SNPs are confirmed employing a validated method know as Pyrosequencing (Pyrosequencing, Westborough, MA). Detailed protocols for Pyrosequencing can be found in: Alderborn et al. Determination of Single Nucleotide Polymorphisms by Real-time Pyrophosphate DNA Sequencing. (2000). *Genome Research.* 10, Issue 8, August. 1249-1265. In brief, Pyrosequencing is a real time primer extension process of genotyping. This protocol takes double-stranded, biotinylated PCR products from genomic DNA samples and binds them to streptavidin beads. These beads are then denatured producing single stranded bound DNA. SNPs are characterized utilizing a technique based on an indirect bioluminometric assay of pyrophosphate (PPi) that is released from each dNTP upon DNA chain elongation. Following Klenow polymerase-mediated base incorporation, PPi is released and used as a substrate, together with adenosine 5'-phosphosulfate (APS), for ATP sulfurylase, which results in the formation of ATP. Subsequently, the ATP accomplishes the conversion of luciferin to its oxi-derivative by the action of luciferase. The ensuing light output becomes proportional to the number of added bases, up to about four bases. To allow processivity of the method dNTP excess is degraded by apyrase, which is also present in the starting reaction mixture, so that only dNTPs are added to the template during the sequencing. The process has been fully automated and adapted to a 96-well format, which allows rapid screening of large SNP panels. The DNA and protein sequences for the novel single nucleotide polymorphic variants are reported. Variants are reported individually but any combination of all or a select subset of variants are also included. In addition, the positions of the variant bases and the variant amino acid residues are underlined.

Results

Variants are reported individually but any combination of all or a select subset of variants are also included as contemplated NOVX embodiments of the invention.

NOV1a SNP data:

NOV1a has four SNP variants, whose variant positions for its nucleotide and amino acid sequences is numbered according to SEQ ID NOs:1 and 2, respectively.

Table 23. cSNP and Coding Variants for NOV1

NT Position of cSNP	Wild Type NT	Variant NT	Amino Acid position	Amino Acid Change
3082	G	A	1028	Ala-Thr
3120	G	A	Silent	Silent
3251	T	C	1084	Val-Ala
4085	A	G	1362	Asp-Gly

NOV4a SNP data:

NOV4a has five SNP variants, whose variant positions for its nucleotide and amino acid sequences is numbered according to SEQ ID NOs:11 and 12, respectively.

Table 24. cSNP and Coding Variants for NOV4

NT Position of cSNP	Wild Type NT	Variant NT	Amino Acid position	Amino Acid Change
321	C	A	Silent	Silent
566	A	C	174	Asn-Thr
751	T	C	236	Phe-Leu
770	T	C	242	Val-Ala
1702	A	G	Silent	silent

NOV6a SNP data:

NOV6a has nine SNP variants, whose variant positions for its nucleotide and amino acid sequences is numbered according to SEQ ID NOs:27 and 28, respectively.

Table 25. cSNP and Coding Variants for NOV6a

NT Position of cSNP	Wild Type NT	Variant NT	Amino Acid position	Amino Acid Change
3093	C	T	986	Thr-Met
3128	C	T	998	Pro-Ser
Insertion before 3145	-	G	1003-end	Discordant
Insertion before 3195	-	C	1020-end	Discordant
Insertion before 3322	-	C	1062-end	Discordant
3376	-	C	1080-end	Discordant

3378	-	C	1081-end	Discordant
Insertion before 3419	-	C	1095-end	Discordant
3559	C	T	Silent	Silent

NOV7 SNP data:

NOV7 has two SNP variants, whose variant positions for its nucleotide and amino acid sequences is numbered according to SEQ ID NOs:35 and 36, respectively.

Table 26. cSNP and Coding Variants for NOV7

NT Position of cSNP	Wild Type NT	Variant NT	Amino Acid position	Amino Acid Change
455	G	A	Silent	Silent
624	A	G	208	Ser-Gly

NOV8 SNP data:

NOV8 has two SNP variants, whose variant positions for its nucleotide and amino acid sequences is numbered according to SEQ ID NOs:37 and 38, respectively.

Table 27. cSNP and Coding Variants for NOV8

NT Position of cSNP	Wild Type NT	Variant NT	Amino Acid position	Amino Acid Change
149	T	C	Silent	Silent
237	A	G	72	Arg-Gly

NOV10a SNP data:

NOV10a has two SNP variants, whose variant positions for its nucleotide and amino acid sequences is numbered according to SEQ ID NOs:41 and 42, respectively.

Table 28. cSNP and Coding Variants for NOV8

NT Position of cSNP	Wild Type NT	Variant NT	Amino Acid position	Amino Acid Change
1677	A	G	438	Asp-Gly
1771	C	G	469	Asn-Lys

EXAMPLE 4. PCR CLONING OF NOV6B

The cDNA coding for a domain of CG50215-03 from residue 436 to 975 was targeted for "in-frame" cloning by PCR. The PCR template is based on human cDNA(s).

The following oligonucleotide primers were used to clone the target cDNA sequence:

F3 5'-AAGCTT TGTCAGCGCAACCCCCAGGTCTGCGGCCCAGG-3 (SEQ ID NO: 155)

F5 5'-CTCGAG ACAGCGTCCAGTCATGGGGTCAAACTCTTCC-3' (SEQ ID NO: 156)

For downstream cloning purposes, the forward primer includes an in-frame HindIII restriction site and the reverse primer contains an in-frame XhoI restriction site.

Two parallel PCR reactions were set up using a total of 0.5-1.0 ng human pooled cDNAs as template for each reaction. The pool is composed of 5 micrograms of each of the following human tissue cDNAs: adrenal gland, whole brain, amygdala, cerebellum, thalamus, bone marrow, fetal brain, fetal kidney, fetal liver, fetal lung, heart, kidney, liver, lymphoma, Burkitt's Raji cell line, mammary gland, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small Intestine, spleen, stomach, thyroid, trachea, uterus.

When the tissue of expression is known and available, the second PCR was performed using the above primers and 0.5ng-1.0 ng of one of the following human tissue cDNAs:

skeleton muscle, testis, mammary gland, adrenal gland, ovary, colon, normal cerebellum, normal adipose, normal skin, bone marrow, brain amygdala, brain hippocampus, brain substantia nigra, brain thalamus, thyroid, fetal lung, fetal liver, fetal brain, kidney, heart, spleen, uterus, pituitary gland, lymph node, salivary gland, small intestine, prostate, placenta, spinal cord, peripheral blood, trachea, stomach, pancreas, hypothalamus.

The reaction mixtures contained 2 microliters of each of the primers (original concentration: 5 pmol/ul), 1 microliter of 10mM dNTP (Clontech Laboratories, Palo Alto CA) and 1 microliter of 50xAdvantage-HF 2 polymerase (Clontech Laboratories) in 50 microliter-reaction volume. The following reaction conditions were used:

PCR condition 1:

a) 96°C 3 minutes

b) 96°C 30 seconds denaturation

c) 60°C 30 seconds, primer annealing

d) 72°C 6 minutes extension

Repeat steps b-d 15 times

e) 96°C 15 seconds denaturation

f) 60°C 30 seconds, primer annealing

g) 72°C 6 minutes extension

Repeat steps e-g 29 times

e) 72°C 10 minutes final extension

PCR condition 2:

a) 96°C 3 minutes

b) 96°C 15 seconds denaturation

c) 76°C 30 seconds, primer annealing, reducing the temperature by 1 °C per cycle

d) 72°C 4 minutes extension

Repeat steps b-d 34 times

e) 72°C 10 minutes final extension

An amplified product was detected by agarose gel electrophoresis. The fragment was gel-purified and ligated into the pCR2.1 vector (Invitrogen, Carlsbad, CA) following the manufacturer's recommendation. Twelve clones per PCR reaction were picked and sequenced. The inserts were sequenced using vector-specific M13 Forward and M13 Reverse primers and the following gene-specific primers:

SF1: GAGAACACGCCAGGCAGCTT (SEQ ID NO: 157)

SF2: CTCCTTTCACTGTGCCTGCCC (SEQ ID NO: 158)

SF3: TGTCCTTCTGGCCACCACC (SEQ ID NO: 159)

SF4: GAGCCTCTTGCCTCGACGTTGACGAGT (SEQ ID NO: 160)

SF5: GTGTCCGGGACTGCGATCCT (SEQ ID NO: 161)

SR1: CGGTGGCACTCGTCCACAT (SEQ ID NO: 162)

SR2: CTGCCGTGTTGTCACAGCG (SEQ ID NO: 163)

SR3: AGGCCCTGCACTGGAAGGA (SEQ ID NO: 164)

SR4: GTCGGTAGCCAGGGGCACAAGTA (SEQ ID NO: 165)

SR5: AGTCCCGGACACAGCGGTA (SEQ ID NO: 166)

The insert assembly 197188002 was found to encode an open reading frame between residues 436 and 975 of the target sequence CG50215-03. 197188002 differs from the original sequence at 2 nucleotide positions and 2 amino acid positions.

The cDNA coding for a domain of CG50215-03 from residue 40 to 345 was targeted for "in-frame" cloning by PCR. The PCR template is based on human cDNA(s).

The following oligonucleotide primers were used to clone the target cDNA sequence:

F2 5'-AAGCTT TGTCCCTTGATCTGTCACAATGGCGGTGTGTGC-3' (SEQ ID NO: 167)

R2 5'-CTCGAG GATCTCCCGGAAACCCTCTGAGCCGAAGGG-3' (SEQ ID NO: 168)

For downstream cloning purposes, the forward primer includes an in-frame HindIII restriction site and the reverse primer contains an in-frame XhoI restriction site.

Two parallel PCR reactions were set up using a total of 0.5-1.0 ng human pooled cDNAs as template for each reaction. The pool is composed of 5 micrograms of each of the

following human tissue cDNAs: adrenal gland, whole brain, amygdala, cerebellum, thalamus, bone marrow, fetal brain, fetal kidney, fetal liver, fetal lung, heart, kidney, liver, lymphoma, Burkitt's Raji cell line, mammary gland, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small Intestine, spleen, stomach, thyroid, trachea, uterus.

When the tissue of expression is known and available, the second PCR was performed using the above primers and 0.5ng-1.0 ng of one of the following human tissue cDNAs:

skeleton muscle, testis, mammary gland, adrenal gland, ovary, colon, normal cerebellum, normal adipose, normal skin, bone marrow, brain amygdala, brain hippocampus, brain substantia nigra, brain thalamus, thyroid, fetal lung, fetal liver, fetal brain, kidney, heart, spleen, uterus, pituitary gland, lymph node, salivary gland, small intestine, prostate, placenta, spinal cord, peripheral blood, trachea, stomach, pancreas, hypothalamus.

The reaction mixtures contained 2 microliters of each of the primers (original concentration: 5 pmol/ul), 1 microliter of 10mM dNTP (Clontech Laboratories, Palo Alto CA) and 1 microliter of 50xAdvantage-HF 2 polymerase (Clontech Laboratories) in 50 microliter-reaction volume. The following reaction conditions were used:

PCR condition 1:

a) 96°C 3 minutes

b) 96°C 30 seconds denaturation

c) 60°C 30 seconds, primer annealing

d) 72°C 6 minutes extension

Repeat steps b-d 15 times

e) 96°C 15 seconds denaturation

f) 60°C 30 seconds, primer annealing

g) 72°C 6 minutes extension

Repeat steps e-g 29 times

e) 72°C 10 minutes final extension

PCR condition 2:

a) 96°C 3 minutes

b) 96°C 15 seconds denaturation

c) 76°C 30 seconds, primer annealing, reducing the temperature by 1 °C per cycle

d) 72°C 4 minutes extension

Repeat steps b-d 34 times

e) 72°C 10 minutes final extension

An amplified product was detected by agarose gel electrophoresis. The fragment was gel-purified and ligated into the pCR2.1 vector (Invitrogen, Carlsbad, CA) following the manufacturer's recommendation. Twelve clones per PCR reaction were picked and sequenced. The inserts were sequenced using vector-specific M13 Forward and M13 Reverse primers and the following gene-specific primers:

SF1: GGCAGCGCCCTACACGGT (SEQ ID NO: 169)

SF2: GATGAGTGCGCGACTGGC (SEQ ID NO: 170)

SR1: CCTCAGCGTCCGCCTCCT (SEQ ID NO: 171)

SR2: CGCACTCATCCACATCTTCGC (SEQ ID NO: 172)

The insert assemblies 197187970, 197187982, and 197187990 were all found to encode an open reading frame between residues 40 and 345 of the target sequence CG50215-03. The cloned insert of assembly 197187982 is 100% identical to the original sequence. 197187970 differs from the original sequence at 2 nucleotide positions and 1 amino acid position. 197187990 differs from the original sequence at 1 nucleotide position and one amino acid position.

OTHER EMBODIMENTS

Although particular embodiments have been disclosed herein in detail, this has been done by way of example for purposes of illustration only, and is not intended to be limiting with respect to the scope of the appended claims, which follow. In particular, it is contemplated by the inventors that various substitutions, alterations, and modifications may be made to the invention without departing from the spirit and scope of the invention as defined by the claims. The choice of nucleic acid starting material, clone of interest, or library type is believed to be a matter of routine for a person of ordinary skill in the art with knowledge of the embodiments described herein. Other aspects, advantages, and modifications considered to be within the scope of the following claims.